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SURGERY

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SURGERY

VOL. 40 NOVEMBER, 1956 No. 5

Original Communications

TOTAL RESECTION OF THE AORTIC ARCH

OSCAR CREECH, JR., M.D., MICHAEL E. DEBAKEY, M.D., AND DANIEL E. MAHAFFEY, M.D., HOUSTON, TEX.

(From the Cora and Webb Mading Department of Surgery, Baylor University College of Medicine, and the Jefferson Davis and Veterans Administration Hospitals)

RESECTION is now a well-established method of treatment of aneurysms involving the distal arch, descending thoracic and abdominal portions of the aorta. Attempts at total resection of the arch have been delayed, however, because of the danger of ischemic changes to the central nervous system from temporary occlusion of arterial trunks arising from the arch. In addition, cross-clamping the ascending aorta proximal to the innominate artery imposes serious strain on the left ventricle. Although hypothermia apparently affords protection against temporary ischemia of the spinal cord during resection of segments of the descending aorta,[7] it is unlikely that this measure alone would protect the brain adequately if the cerebral circulation were occluded. To overcome these deterring factors, temporary shunts have been devised to permit exclusion of the entire aortic arch without interfering appreciably with cerebral blood flow or cardiac output.

Hardin, Batchelder, and Schafer[5] employed multiple small bore (1.14 to 2.69 mm.) polyethylene tubes as experimental aortic by-pass shunts, and Schafer and Hardin[8] reported unsuccessful application of this method in one patient whose aortic arch was resected. On the basis of experimental data,[1, 6] Stranahan and associates[9] utilized a by-pass shunt, with an inside diameter of 10 mm. from ascending to descending aorta in performing total removal of the aortic arch. The patient succumbed, however, with evidence of cerebral damage (right hemiplegia). A third case of total resection of an aneurysm of the aortic arch was reported by Cooley, Mahaffey, and DeBakey,[2] who employed a shunt of compressed polyvinyl sponge (Ivalon) with an inside diameter of 14 mm. Thrombosis developed in one of the carotid shunts, and, although the patient survived for six days, he never regained consciousness.

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Recently we have performed total excision of the aortic arch in two patients who survived operation with no evidence of ischemic damage to brain or spinal cord, only to succumb from complications on the first and twelfth postoperative days, respectively. The size of the aneurysm in each case made it necessary to employ somewhat different techniques to maintain cerebral blood flow during operation. Since these methods of temporarily by-passing the aortic arch are different from those previously described and may be applicable in a variety of circumstances, these cases are presented in detail.

CASE REPORTS

CASE 1.—A Negro man, 60 years old, was admitted to the Houston Veterans Administration Hospital on July 20, 1955. Two years previously hoarseness had developed, and, shortly thereafter, shortness of breath. A roentgenogram of the chest disclosed an aneurysm of the arch of the aorta, and the patient was referred to this hospital for treatment.

Fig. 1.—Case 1. Angiocardiogram showing a fusiform aneurysm of the aortic arch. The ascending and descending aorta are of normal diameter.

The patient had had a penile lesion while on active duty during World War I. Despite antisyphilitic therapy at the time, the result of the serologic test for syphilis remained positive, and three years prior to admission he had a second course of antisyphilitic therapy. In November, 1954, because of a persistently positive reaction to the serologic test for syphilis, he was given 6,000,000 units of penicillin during a period of ten days. At that time angiocardiographic examination (Fig. 1) revealed a well-defined saccular aneurysm projecting downward from the lesser curvature of the aortic arch. The diameter of the ascending and descending segments of the aorta appeared normal.

On the present admission the blood pressure was 120 mm. Hg systolic and 80 mm. Hg diastolic. Examination revealed left vocal cord paralysis, slight deviation of the trachea to the right, and prominent pulsations in both the first and second intercostal spaces bilaterally. With the exception of a soft apical systolic murmur, the heart sounds were

of normal quality, and there was no evidence of cardiac enlargement. Laboratory studies revealed a negative reaction to the serologic test for syphilis, normal hemogram, and blood urea nitrogen of 15 mg. per 100 c.c. Lee-White clotting time and bleeding time were within normal limits. Electrocardiograms showed a normal sinus rhythm and no significant abnormalities. Posteroanterior roentgenogram of the chest (Fig. 2, *A*) disclosed mediastinal mass projecting toward the left, the borders of which were smooth and flecked with calcium except for a small projection at the level of the second left anterior intercostal space. The trachea was deviated slightly to the right, and the diaphragms were in normal position. In the left lateral view, (Fig. 2, *B*) the mass appeared to arise from the underside of the transverse arch. The aneurysm appeared to be confined to the transverse portion of the aortic arch and interposed between ascending and descending aortic segments of relatively normal diameter. There was no evidence of bony erosion.

On July 26, 1955, resection of the aneurysm was attempted. Anesthesia was induced with intravenous barbiturate and succinyl citraline and nitrous oxide and oxygen. The patient was then immersed in a tub of ice water. It was soon apparent that the depth of anesthesia was inadequate, as evidenced by shivering. In an attempt to correct this, the plane of anesthesia was deepened with high concentrations of ether, and cardiac arrest shortly ensued. The left side of the chest was opened immediately, and the heart was found to be in asystole. Cardiac massage was promptly begun, and 5 c.c. of a 10 per cent solution of calcium chloride was injected into the left ventricle. Vigorous cardiac action returned promptly and persisted. Hurried examination of the aneurysm confirmed the angiocardiographic findings and further supported the belief that excision was feasible.

The patient recovered fully from this unfortunate incident except for persistence of moderate left hemothorax. Transient T-wave changes appeared on subsequent electrocardiograms, but they reverted to normal within the next seven days.

On Aug. 5, 1955, the patient was again anesthetized, and general body hypothermia was induced by immersion in an ice-alcohol bath. When the rectal temperature reached 91.5° F. (after about one hour), he was removed from the bath and the operation was begun. With the patient in a supine position and tilted 10 degrees to the right and with the left arm suspended, incisions were made through the third anterior interspaces on both sides, transecting the sternum. Median sternotomy was done; this formed an inverted-T incision which afforded excellent exposure of the region of the aortic arch and great vessels (Fig. 3, *A*). The residual clotted hemothorax was evacuated. The left phrenic nerve was isolated and retracted with a tape, and the fibro-fatty tissue in the anterior mediastinum was dissected from the anterior aspect of the great vessels to expose the pericardium, which was reflected off the ascending aorta and pulmonary artery. The position of the aneurysm was such that aortorrhaphy could not be performed; however, excision of the entire arch with restoration of continuity by a homograft seemed feasible. Tapes were first passed about the various vessels to aid in their proximal and distal control while subsequent dissection was done (Fig. 3, *B*). The visceral pericardium was then excised from the anterior surface of the ascending aorta, and a noncrushing exclusion clamp was applied. A previously prepared shunt, made of compressed polyvinyl sponge (Ivalon), having an internal diameter of 14 mm. and a single lateral branch in its center, was sutured to the excluded portion of proximal aorta in an end-to-side fashion (Fig. 3, *C*). In a similar manner, a portion of the descending aorta was excluded, and the distal end of the shunt was implanted (Fig. 3, *D*). Upon release of the exclusion clamps, there was satisfactory flow of blood through the shunt. Occlusion of the ascending aorta distal to the shunt caused a decrease in the pulsations of the carotid arteries, which were filling in a retrograde fashion. By partial occlusion of the descending aorta distal to the shunt with a second clamp, the carotid pulses were restored to normal volume. Again with partial exclusion clamps, the right and left carotid arteries were joined by insertion of a short (2.5 cm.) arterial homograft approximately 1 cm. in diameter. Upon completion of this shunt, either the innominate or the left carotid artery could be occluded at its origin without altering the carotid pulses (Fig. 4, *A*). Next, the ascending aorta was doubly clamped just distal to the shunt and divided. The innominate artery was similarly occluded and divided. Cerebral blood flow was now maintained by way of the aortic shunt, retrograde

B.

A.

Fig. 2.—Case 1. Posteroanterior roentgenogram of the chest (*A*) showing an aneurysm of the aortic arch displacing the trachea to the right. The left lateral wall of the aneurysm is faintly outlined by flecks of calcium. In the left lateral projection (*B*) the aneurysm extends downward to the region of the pulmonary artery.

through the aortic arch, through the left carotid artery and intercarotid shunt, to the brain (Fig. 4, *B*). The reconstituted arch homograft was first sutured to the innominate artery and then the proximal aortic anastomosis was performed (Fig. 4, *C*). A noncrushing clamp was placed across the graft between the innominate and left carotid branches. and when the occluding clamp was removed from the ascending aorta, blood flowed through

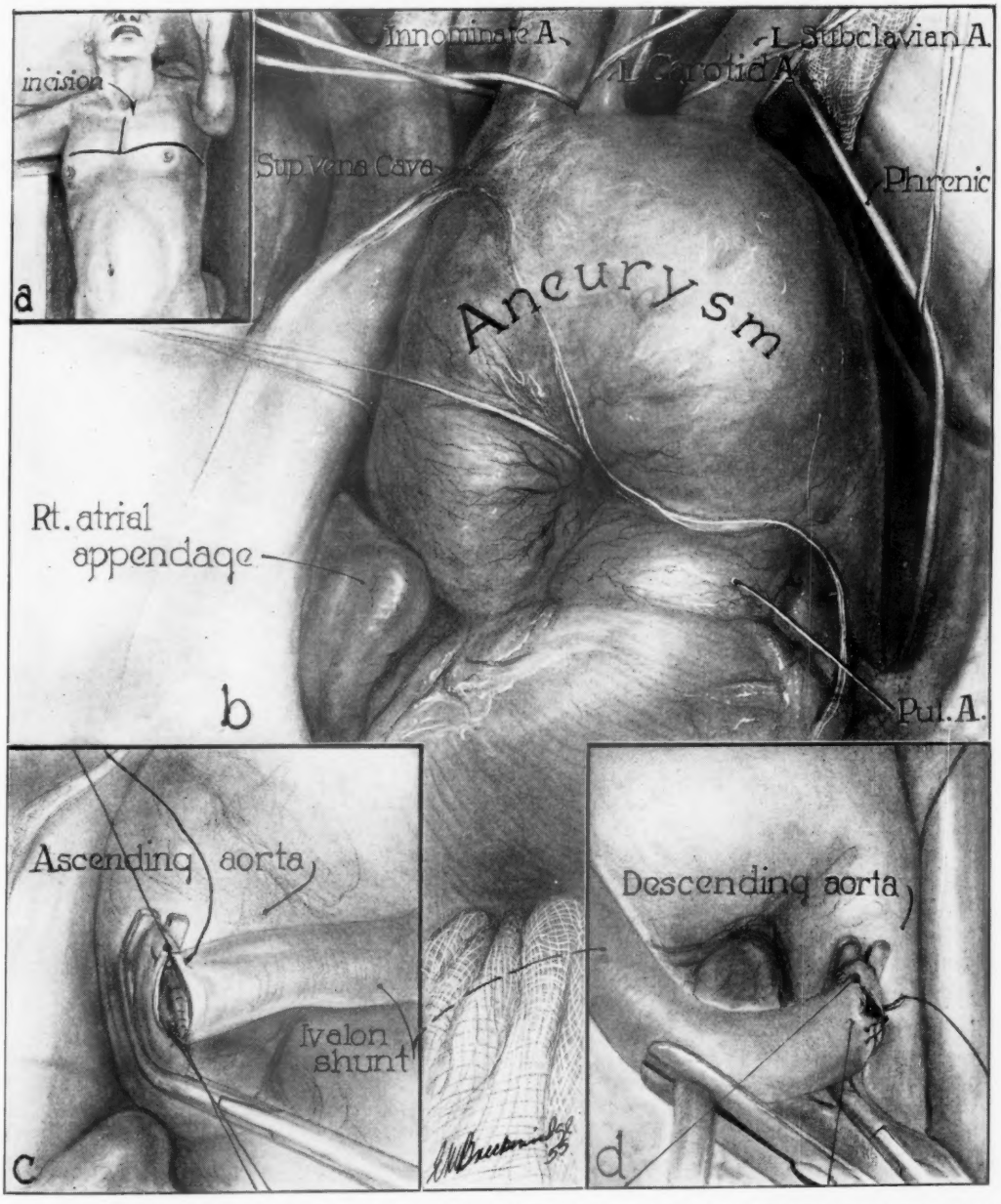


Fig. 3.—Case 1. Drawings made at operation showing (*A*) the incisions employed, (*B*) the aneurysm of the aortic arch and its relation to the innominate, carotid, subclavian, and pulmonary arteries, and (*C*) the technique of anastomosis of the shunt to ascending and (*D*) descending aorta.

the proximal portion of the graft, into the innominate artery, and through the intercarotid shunt to the left common carotid artery. The left common carotid and subclavian arteries and the aorta distal to the aneurysm were occluded, and the aneurysm was removed, except for a small portion of its posterior wall that was intimately adherent to the pulmonary

artery. The left common carotid was then anastomosed to the graft (Fig. 4, *D*) and the nonerushing clamp was moved to a point just distal to the left carotid, so that blood flowed into the carotid vessels in a normal fashion (Fig. 4, *E*). Because of a discrepancy in length of the left subclavian artery, it was necessary to suture a small homograft to its proximal end so that it could be anastomosed to the arch without tension. The aorta was then occluded distal to the subclavian and the clamps on the subclavian artery were removed. The remaining anastomosis between graft and distal aorta was accomplished (Fig. 4, *F*), and upon removal of the clamps normal blood flow through the aortic arch and

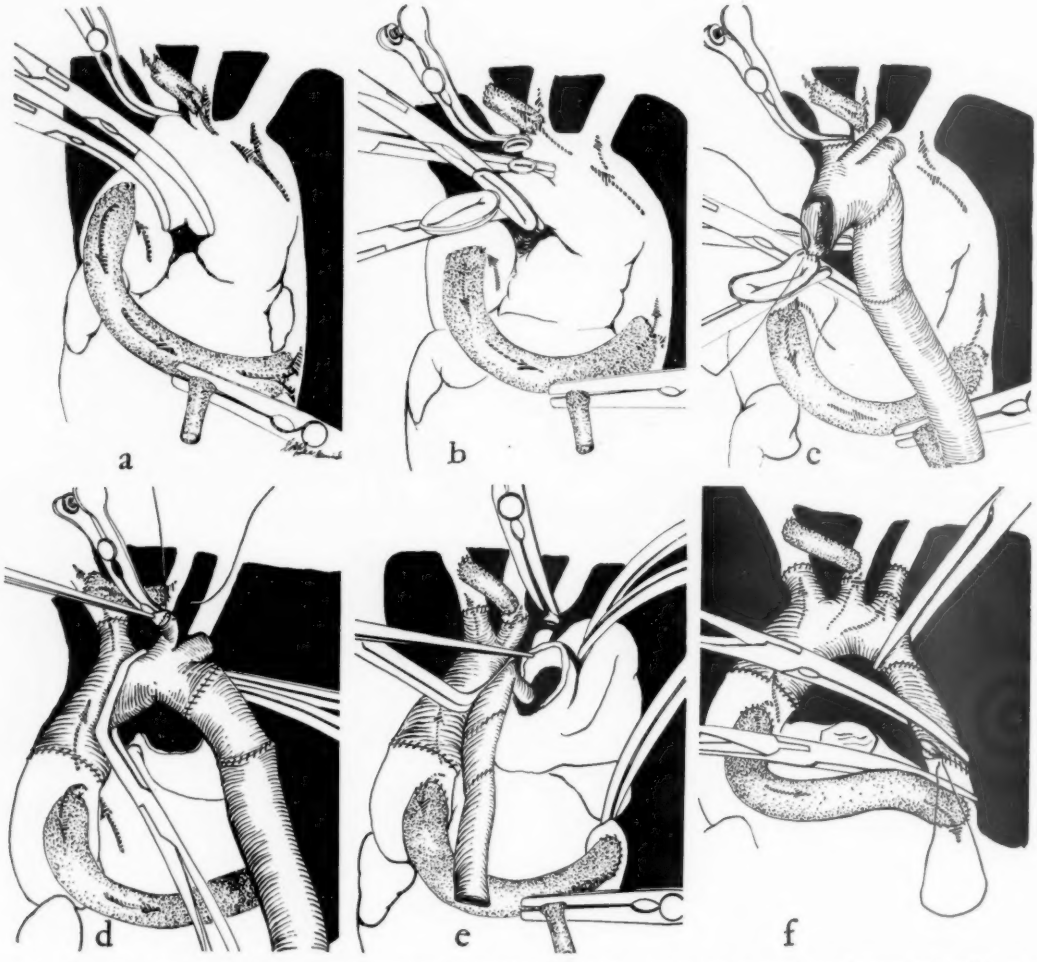


Fig. 4.—Case 1. The technique of resection of the aortic arch and replacement with a homograft is shown diagrammatically. An intercarotid shunt is implanted and the innominate artery and ascending aorta occluded (*A*) and divided (*B*). The direction of blood flow is indicated by arrows. The innominate branch of the homograft is anastomosed first, followed by the ascending aorta (*C*) and the left carotid (*D*). The aneurysm is then excised (*E*), and the subclavian and descending thoracic anastomoses are performed (*F*).

its branches was established. The Ivalon by-pass was removed, and these incisions in the proximal and distal aorta were closed. The homograft connecting the carotid arteries was left in place (Fig. 5). The thoracic wall was closed after insertion of catheters into each pleural space for water-seal drainage. The divided sternum was immobilized with wire sutures, the muscles and fascia were approximated with chromic catgut, and the skin was closed with silk.

Anesthetization was begun at 7:00 A.M. and was continued for approximately 1 hour and 45 minutes, after which the patient was maintained on oxygen alone. Body temperature was reduced to 91.5° F. after 60 minutes of immersion in the ice-alcohol bath, and subse-

quently drifted to 82° F. Operation required 11½ hours, having been begun at 9:20 A.M. and completed at 8:50 P.M. The blood pressure fell from a precooling level of 120/80 mm. Hg to approximately 70/50 mm. Hg, where it remained throughout the procedure. The pulse rate fell from 105 to 60 beats per minute. Rewarming was accomplished with a Therm-o-Rite Blanket.

The patient began to react within 30 minutes following completion of the operation, although his temperature was only 91° F., and at 10:00 P.M. he responded to questions and moved all extremities. Approximately two hours after operation the patient indicated that the endotracheal tube was uncomfortable, and as the respiratory exchange appeared

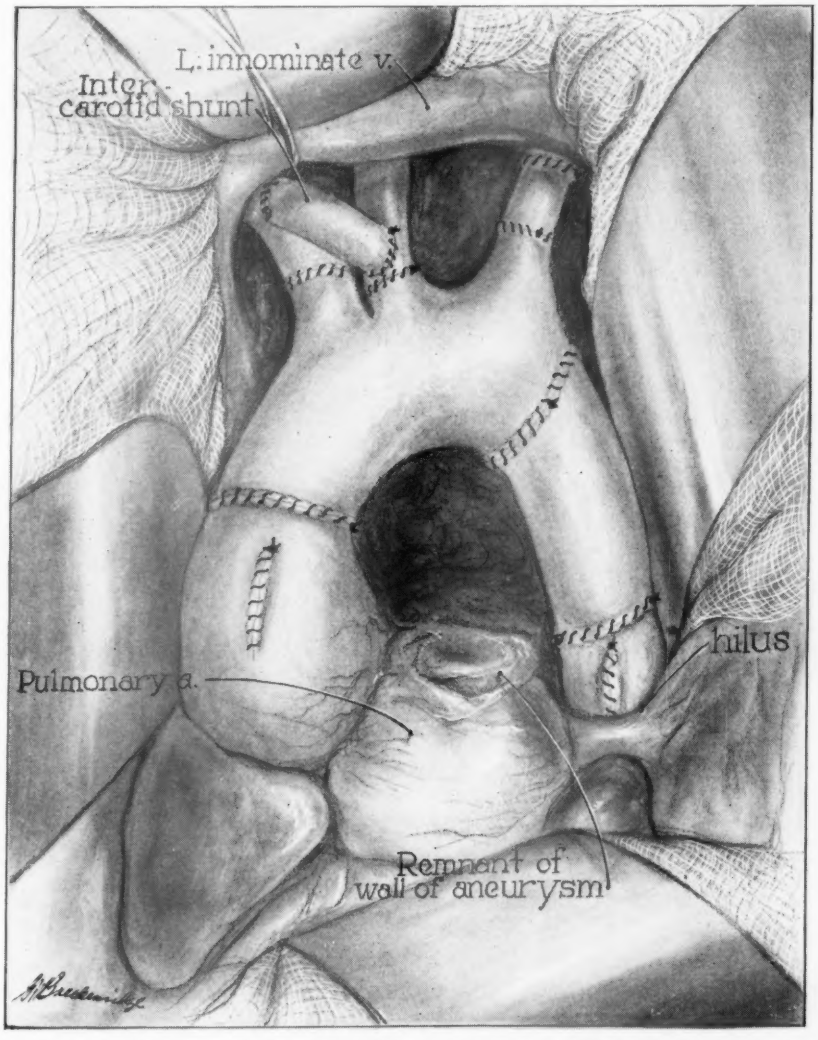
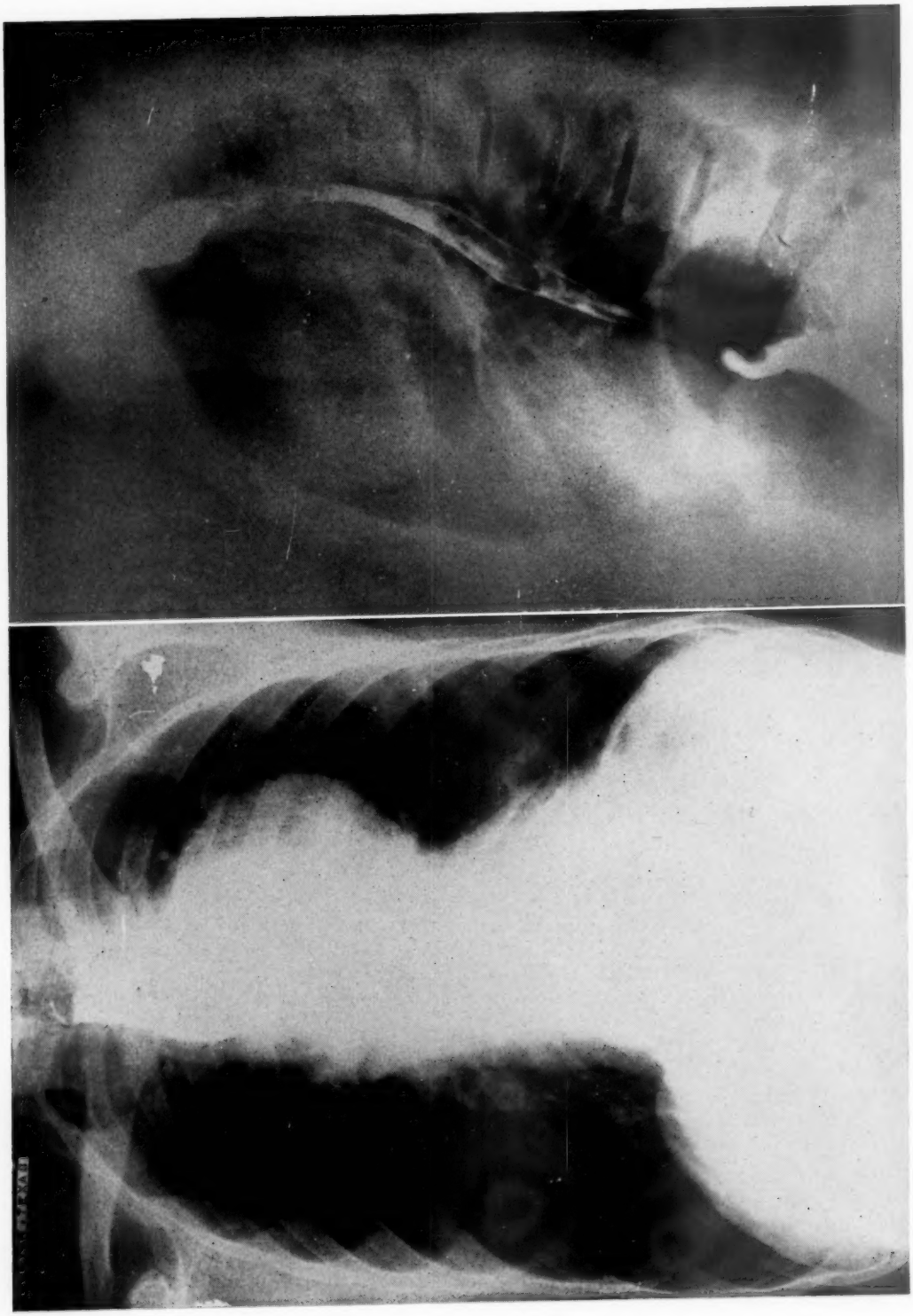


Fig. 5.—Case 1. Drawing made at operation showing completion of the arch replacement. The aortic shunt has been removed and the intercarotid shunt remains.

adequate the tube was removed. Breath sounds were normal over the right side of the chest but diminished over the left. A roentgenogram revealed good aeration of both lungs, slight elevation of the left hemidiaphragm, and moderate deviation of the trachea to the right. About three hours after operation, the patient was alert and talking freely, and appeared to have reacted fully. His temperature had returned to normal after about four hours of rewarming. At 4 A.M. his blood pressure suddenly dropped to 60/40 mm. Hg and his respiration, which had been slightly rapid, became definitely labored. Endotracheal aspiration and an infusion of norepinephrine failed to produce improvement. A



A. *B.*

Fig. 6.—Case 2. Posteroanterior (*A*) and left lateral (*B*) roentgenograms of the chest showing a fusiform aneurysm of the aortic arch projecting into the left pulmonary field and displacing the esophagus to the right and posterior.

tracheostomy was performed and at the end of this procedure cardiac arrest occurred. The chest was opened on the left side, cardiac massage was begun, and calcium chloride was injected into the left ventricle. An endotracheal tube was introduced, and oxygen was administered. Sustained cardiac action began relatively promptly, but an electrocardiogram revealed idioventricular rhythm. After the heart was observed for about fifteen minutes, its action became stronger and more regular, so the thoracic wound was closed; however, the patient's condition gradually deteriorated, and he died about six hours later.

Necropsy revealed severe atelectasis, bilaterally, with early inflammatory changes in the left lung. The graft and all anastomoses were patent and had apparently functioned satisfactorily until the patient's death. No other significant abnormalities were noted.

Comment.—The shunt employed in this case to divert blood from ascending to descending aorta was made of polyvinyl sponge by a method described previously.[2] With a reduced body temperature, its luminal diameter of 14 mm. provided sufficient blood flow to prevent ischemic changes. A single branch was incorporated into the by-pass as a precautionary measure, should retrograde filling of the carotid arteries prove inadequate. In such an event, anastomosis between the branch of the aortic by-pass and the intercarotid shunt could have been performed.

The method employed to maintain cerebral blood flow was selected because the aneurysm was relatively small and involved principally the inferior surface of the arch. This made it possible to "walk" the graft into place as the aneurysm was being removed. A homograft was used as an intercarotid shunt since this type of arterial replacement has proved most satisfactory for vessels of small caliber. In addition, it could be left in place upon completion of the procedure with little danger of thrombosis or other complication, so that lateral repair of the carotid wall is not necessary.

CASE 2.—A Negro man, 69 years old, was admitted to the Jefferson Davis Hospital on Sept. 21, 1955. One year previously he had developed a cough with a single episode of hemoptysis and subsequently developed pain in the left side of the chest, hoarseness, and dysphagia. A roentgenogram of the chest disclosed an aneurysm of the arch of the aorta and the patient was referred to this hospital for treatment.

There was no history of syphilis, but about thirty years previously the patient had developed lymphogranuloma inguinale.

On admission the blood pressure was 100 mm. Hg systolic and 60 mm. Hg diastolic. There was paralysis of the left vocal cord, a tracheal tug, a grade $\frac{+}{1}$ aortic systolic murmur, and an increase in the retromanubrial dullness. Laboratory studies revealed a normal urinalysis, hemoglobin of 9.5 Gm., hematocrit of 31 per cent, and a blood urea nitrogen of 17 mg. per 100 c.c. There was a positive reaction to the serologic test for syphilis. Posteroanterior and left lateral roentgenograms of the chest revealed an aneurysm of the arch of the aorta projecting anteriorly and to the left, displacing the esophagus posteriorly and to the right (Fig. 6). Angiocardiograms clearly demonstrated an aneurysm involving the entire aortic arch and extending downward from the lesser curvature (Fig. 7). The electrocardiogram was within normal limits.

Prior to operation the patient received 1,000 c.c. whole blood which elevated the hemoglobin and hematocrit to relatively normal levels. On Oct. 1, 1955, operation was performed under general anesthesia. With the patient in the supine position, tilted slightly to the right, and with the left arm suspended, incisions were made through the fourth anterior intercostal spaces on both sides, transecting the sternum (Fig. 8). Medium sternotomy was then performed to the suprasternal notch. The pericardium was opened widely, and the innominate, left carotid, and subclavian arteries were isolated and tapes were passed about them (Fig. 8). The left innominate vein was almost completely

occluded as it crossed in front of the aneurysm, so it was doubly ligated and divided. The aneurysm measured about 12 by 15 cm. and displaced the pulmonary artery posteriorly and inferiorly. The ascending aorta was slightly dilated but was not involved by the aneurysm. The ascending aorta was dissected from the pulmonary artery and a tape passed about it. The descending aorta was isolated at about the level of the seventh thoracic vertebra and a tape passed about it. With the use of exclusion clamps an Ivalon shunt with an internal diameter of 20 mm. and with two posterior branches (heterografts) attached was implanted into the side of the ascending and descending portions of the

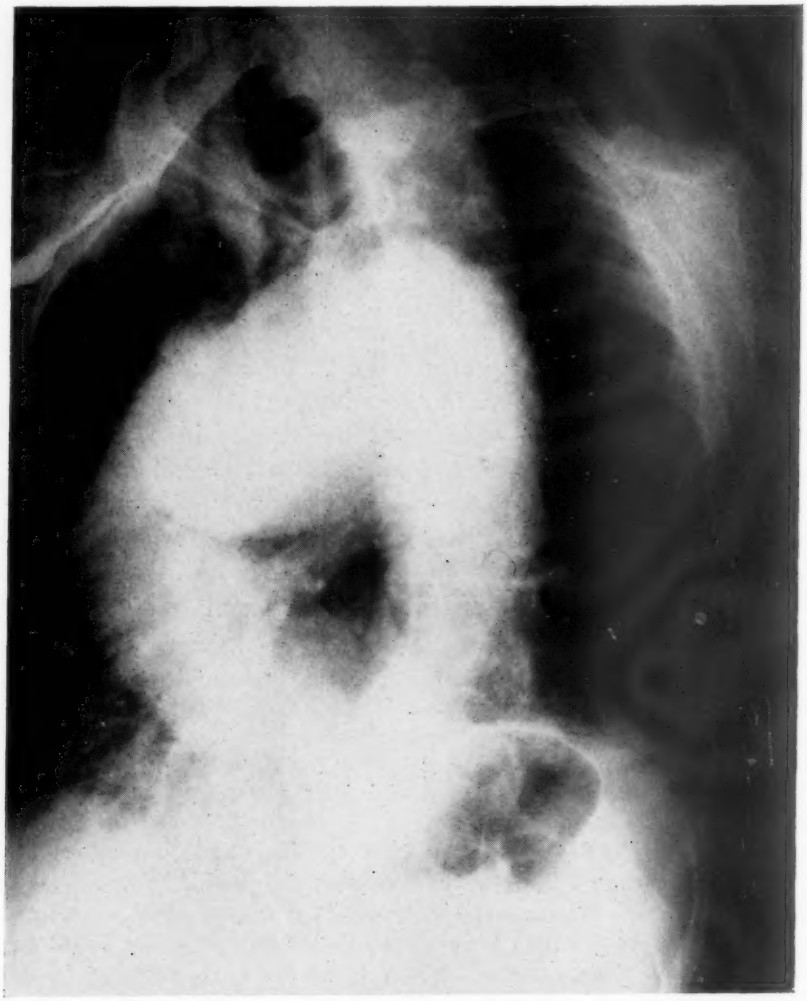


Fig. 7.—Case 2. Angiocardiogram reveals the aneurysm to involve the transverse and descending portions of the aortic arch. The ascending aorta is moderately dilated.

aorta in such a manner that it lay outside of the operative field. The posterior branches of the shunt were then anastomosed to the side of the innominate and left carotid arteries using exclusion clamps (Fig. 9, *A*). Following removal of the clamps the shunt appeared to function satisfactorily. Occluding clamps were then applied to the ascending and descending aorta and to the branches arising from the arch; the aneurysm was opened widely and removed (Fig. 9, *B*). The posterior wall was densely adherent to the vertebral bodies, having displaced the trachea and the esophagus to the right. Inferiorly the wall of the aneurysm had eroded into the main pulmonary artery at the origin of the left branch and this vessel was entered during the dissection. Repair was accomplished readily, however, with interrupted sutures. A lyophilized arch homograft was then implanted with anastomosis of the innominate

branch first, then the ascending aorta, followed by the left carotid, left subclavian, and descending aorta. Following insertion of the homograft, exclusion clamps were reapplied to the ascending and descending portions of the aorta and to the innominate and left carotid arteries and the shunts were removed. The defects in the arteries were then closed with continuous sutures of arterial silk (Fig. 10). The margins of the posterior wall of the

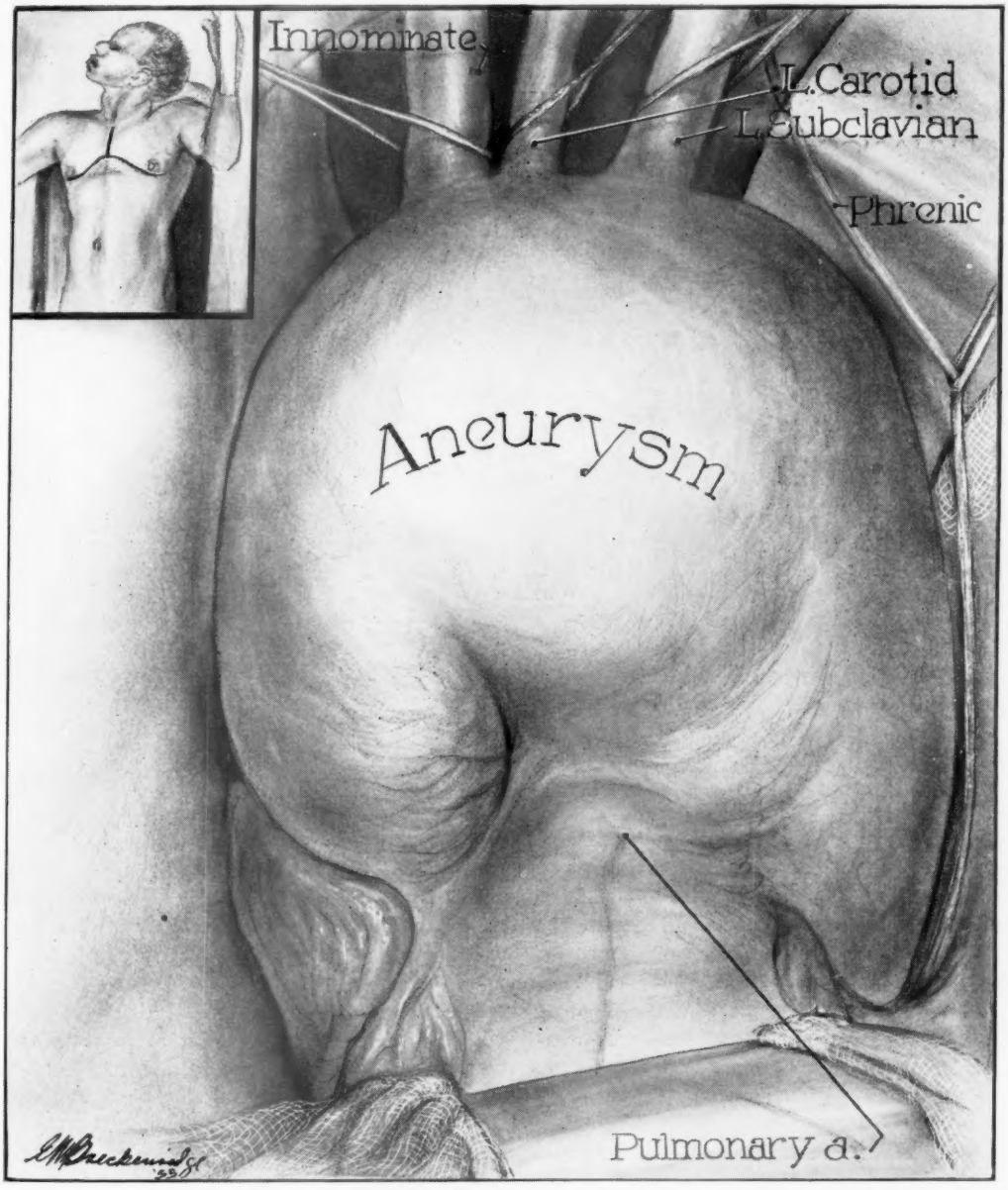


Fig. 8.—Case 2. Drawing made at operation showing the incisions (inset), and the aneurysm and its relation to the pulmonary artery. Note that the ascending aorta is somewhat dilated.

aneurysm which was left in place were then oversewn with a running catgut suture for hemostasis. Remnants of clot were removed and the pericardium was reapproximated loosely. The chest wall was closed after insertion of catheters into each pleural space for water-seal drainage. The divided sternum was immobilized with wire sutures, the muscles and fascia were approximated with chromic catgut, and the skin was closed with silk.

The operation had required about 9½ hours, and during this time the patient's respirations were controlled by means of a Jefferson Ventilator. Approximately 5,000 c.c. of whole blood was administered during the procedure.

The patient reacted promptly from anesthesia and exhibited no evidence of cerebral or spinal cord damage. Excellent pulses were present in all peripheral vessels and vital signs were well maintained. Respirations were assisted by the use of a Halliburton demand-assist valve connected to a special tracheostomy tube fitted with a tracheal balloon.

On the first postoperative day the patient was clinically jaundiced and the serum bilirubin was reported as 11.6 mg. per 100 c.c. On the second postoperative day the chest catheters were removed and roentgenograms of the chest revealed both lungs to be well expanded. On the

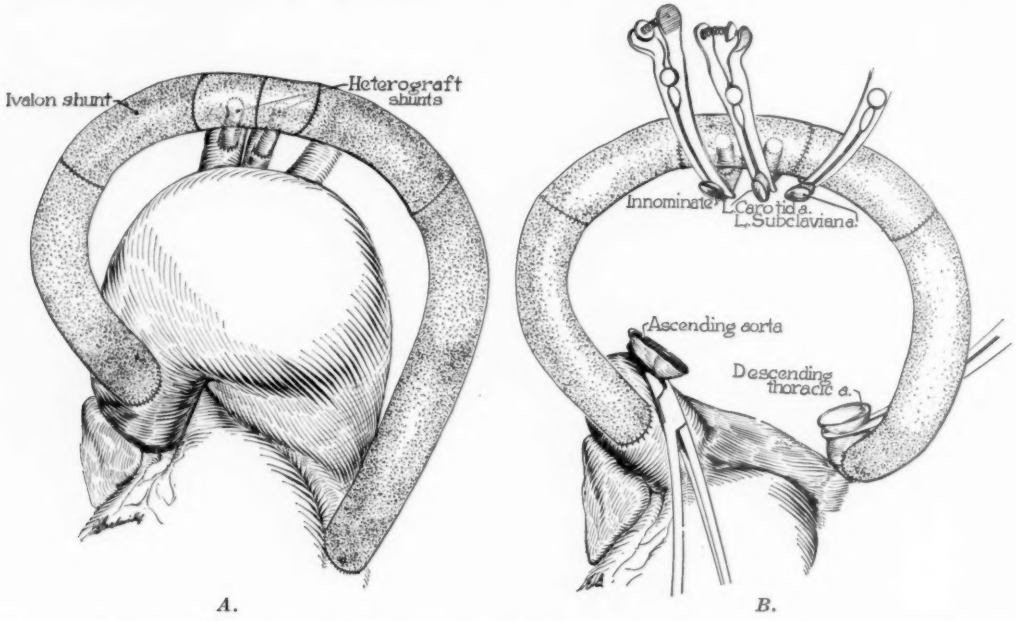


Fig. 9.—Case 2. The aortic and carotid shunts are shown diagrammatically in (*A*) before and in (*B*) after excision of the aneurysm.

fourth postoperative day, because of frequent premature ventricular contractions and tachycardia, the patient was digitalized rapidly and quinidine therapy was begun. Complete digitilization was promptly achieved and a normal sinus rhythm restored. On the fifth postoperative day the temperature rose to 103° F. and on the following day there was definite evidence of infection of the wound. Cultures made from the wound exudate revealed a hemolytic Staphylococcus sensitive to Chloromycetin and erythromycin, so these agents were administered intravenously. The patient appeared to respond to this antibiotic therapy, but on the evening of the seventh postoperative day the left chest wound broke down completely producing an open thoracotomy and necessitating surgical closure of the wound. Thus under general anesthesia the entire wound was opened. The graft was not visualized since the dissection was purposely confined to the anterior mediastinum, but it appeared that the inflammatory process involved only the chest wall. Catheters were placed into both pleural cavities and the wound was again closed. The patient's temperature subsequently fell to normal and he was generally improved. On the ninth postoperative day the patient was taking a regular diet and ambulation was started. However, on the eleventh postoperative day he suddenly began to bleed from the left chest wound and expired rapidly. At necropsy the left pleural space was filled with bright red blood. The site of hemorrhage was found to be a disruption of the innominate branch of the homograft about 0.5 cm. proximal to the anastomosis. At this area the graft was completely disintegrated. Immediately adjacent to the innominate and left carotid arteries there was a small abscess containing about 20 c.c. of purulent material. Cultures of the homograft in this area yielded hemolytic *Staphylococcus aureus.*

Comment.—Because of its large size, removal of the aneurysm was necessary before implantation of the homograft was begun. This precluded utilization of the method employed in Case 1. Instead, separate temporary shunts were anastomosed to the innominate and carotid arteries. The Ivalon shunt was so constructed that it lay on the periphery of the operative field permitting free

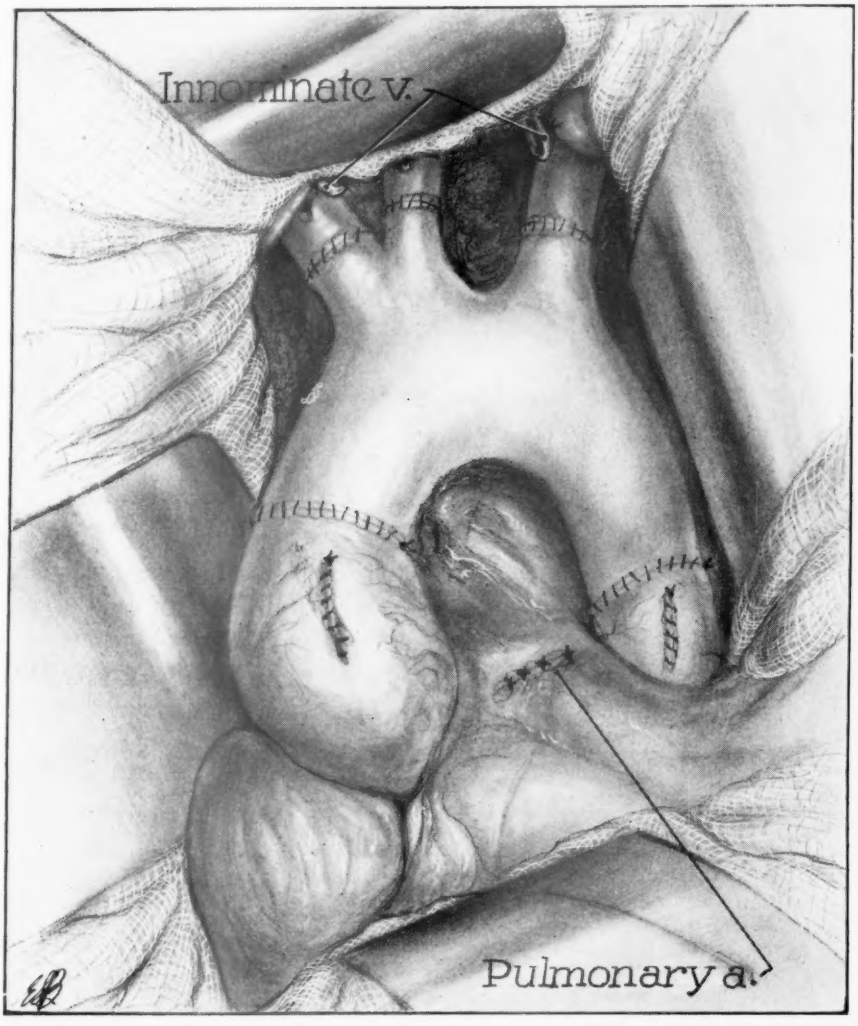


Fig. 10.—Case 2. Drawing made at operation showing completion of the arch replacement. The shunts have been removed.

access to the aneurysm and the branches of the arch. Since the operation was not performed under hypothermia, a larger (20 mm.) shunt was considered necessary to maintain adequate blood flow and to avoid left ventricular strain.

Although there was considerable disproportion between the ascending aorta and the homograft, this was readily overcome by beveling the homograft toward its greater curvature.

DISCUSSION

The methods utilized for temporarily by-passing the arch and for maintaining cerebral blood flow are practical and effective. Hypothermia does not appear to be necessary with either method if a by-pass shunt of 20 mm. is

employed and if there is no interruption of carotid blood flow. In fact, by adding the hazards inherent in hypothermia, particularly when applied in older persons, risk of operation may be increased.

The extensive thoracic incisions necessary for adequate exposure seriously interfere with the chest wall component of ventilation. Added to this is the frequent occurrence of paralysis of the left leaf of the diaphragm as a result of pressure on the phrenic nerve from the aneurysm, or injury to the nerve at operation. As a consequence, ventilatory effort is poor, secretions accumulate, and serious pulmonary complications may ensue. Therefore, tracheostomy and the use of a positive pressure, demand-assist valve are considered essential for the postoperative management of these patients.

In spite of the tragic complications encountered, these two cases demonstrate the feasibility of total excision of the aortic arch without interfering with blood flow to the central nervous system.

SUMMARY

Attempts at total resection of the aortic arch have been delayed because of the dangers of ischemic changes to the central nervous system. To overcome this obstacle, temporary shunts have been devised to permit exclusion of the aortic arch without interfering with cerebral blood flow or cardiac output.

Two cases are reported in which temporary by-pass shunts of polyvinyl sponge were utilized for total resection of the aortic arch for aneurysm. These patients survived one and ten days, respectively, after operation with no evidence of ischemia of the central nervous system. It appears that hypothermia is not necessary when a shunt of 20 mm. internal diameter is employed.

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A MECHANICAL PUMP-OXYGENATOR FOR SUCCESSFUL CARDIOPULMONARY BY-PASS

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THE medical literature bulges with reports of various techniques both experimental and clinical for intracardiac surgery under direct vision. A large segment of these reports deals with heart-lung machines. Björk[3] and Karlson[17] have extensively reviewed this general area of investigation. Andreasen[1, 2] introduced the concept of "azygos" or low flow rates in 1952, and Lillehei[7] adopted this principle to meet the needs of controlled cross circulation. Gibbon[23] and Dennis[9] in this country and Crafoord[8] and Jongbloed[16] in Europe have long researched in the field of mechanical heart-lung devices. Kirklin and Donald[11, 15, 18] recently modified the Gibbon apparatus and applied it with success to clinical cases. Important changes by Campbell[4] in the use of a biologic oxygenator have made this technique relatively safe.

Hypothermia has endured among the various methods for intracardiac surgery primarily as a means of entry to the right atrium. Clinical results by Lewis[19] and Swan[24] on the use of hypothermia for closure of atrial septal defects clearly indicate that perfusion techniques for this procedure are unnecessary. Right ventriculotomy, potentially essential for the repair of any ventricular septal defect, is not well tolerated by the hypothermic heart. At this moment it appears that procedures in which ventriculotomy may be necessary are best performed at normal temperature with some kind of heart-lung substitute.

DESCRIPTION OF HEART-LUNG MACHINE

The cardiac equivalent is a simple finger pump† widely used in physiologic experiments. The oxygenator is of the gas dispersion type suggested by von Euler and Heymans[25] in 1932. Clark and Gollan[5, 13, 14] have described together and singly a similar apparatus. Gimbel,[12] Waud,[26] and Clowes[6] have also reported experiences with bubble oxygenators. Even more recently, Lillehei has abandoned controlled cross circulation for a disposable bubbler conceived by DeWall.[10] The oxygenator investigated in this work is a plastic modification of the unit previously reported in coronary perfusion experiments under hypothermia.[22]

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†Manufactured by Sigmamotor, Middleport, N. Y.

Fig. 1 is a photograph of the oxygenator and combination filter chamber and bubble trap. The oxygenator consists essentially of two cylinders or bubble chimneys concentrically located in a large cylinder or reservoir. Venous blood enters the bubble cylinders through parallel sidearms where it is met by oxygen introduced from below through porcelain filter discs. Bubbles of blood and

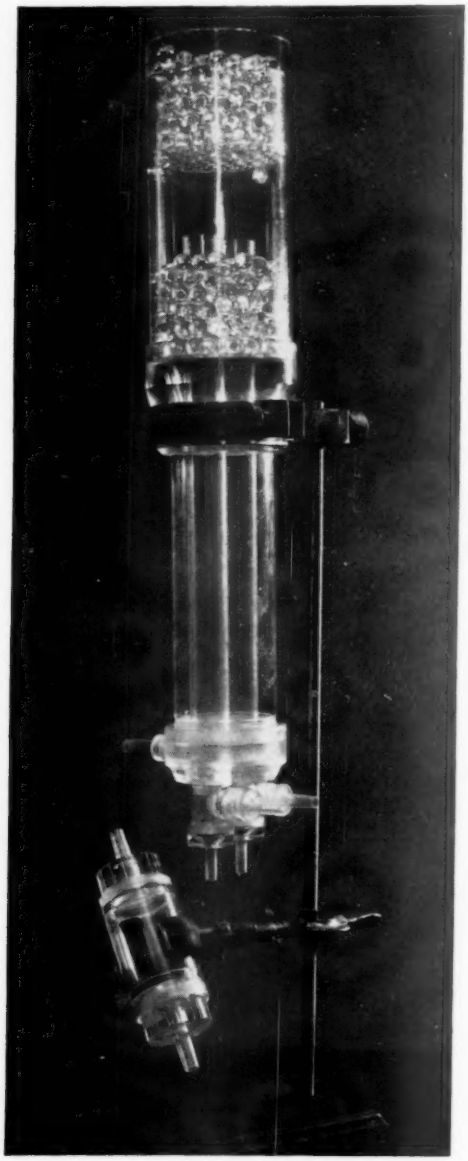

Fig. 1.—Photograph of the plastic oxygenator and filter chamber.

oxygen emerge from the chimneys between two strata of Lucite spheres, one-half inch in diameter, which are coated with Antifoam A spray.* The bubbles break against the spheres, and oxygenated blood then cascades into the outer chamber or reservoir. The entire oxygenator is made of Lucite or Plexiglas

*Dow Corning, Midland, Mich.

(methyl methacrylate) and can be disassembled for cleaning. Sterilization is effected by immersion in Zephiran chloride solution since high temperatures warp the material. Oxygenation with this instrument is simple, efficient,

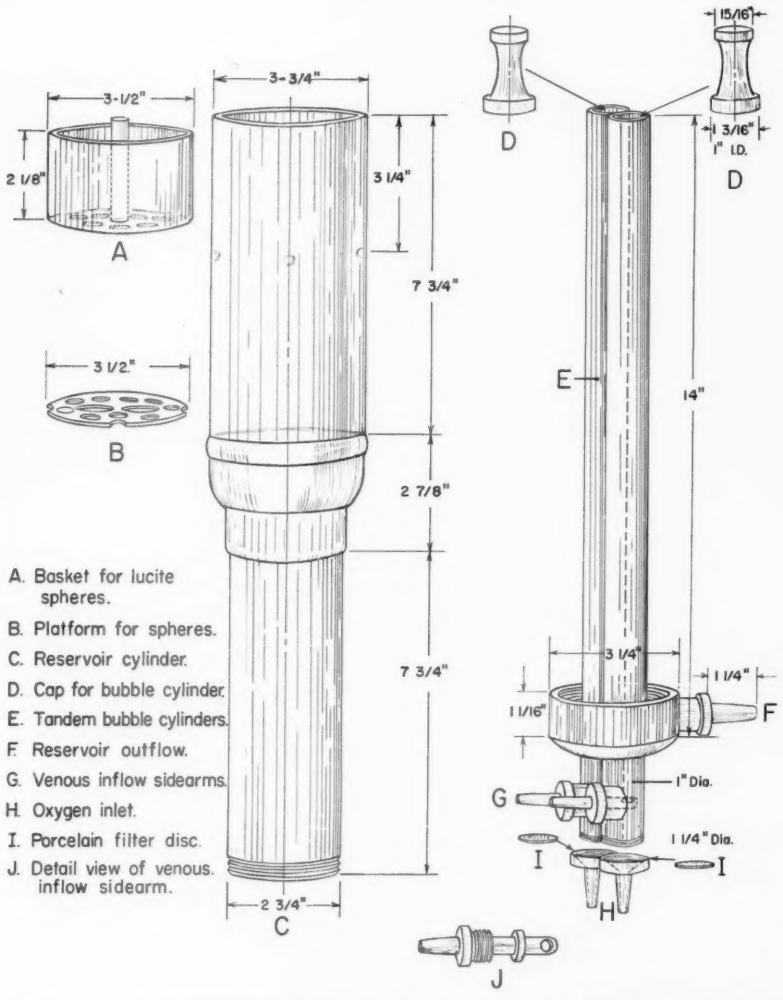

Fig. 2.—Drawing of the oxygenator showing the principal dimensions and illustrating in general the various parts of the disassembly.

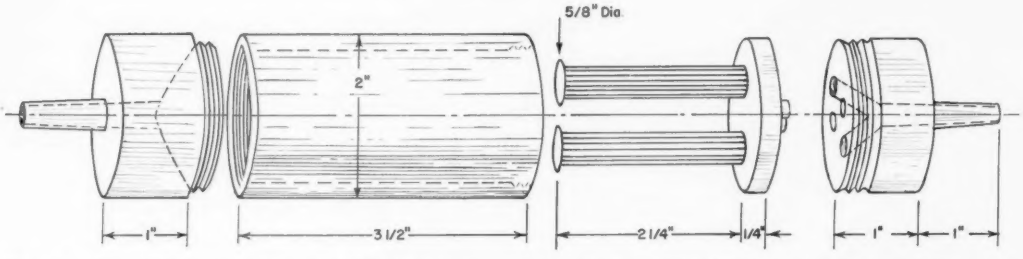

Fig. 3.—The filter chamber and bubble trap consist of four Plexiglas sections in addition to the paired nylon filters.

and complete, and carbon dioxide readily leaves the blood in accordance with Henry's law of partial pressures. Fig. 2 is a drawing of the oxygenator.

The combination filter chamber and bubble trap seen in Fig. 1 is also constructed of Lucite while the filters are nylon. Blood is drawn from the reservoir through the double-barreled filter chamber, then propelled into the arterial side of the circulation. The finger pump is interposed between the filter chamber and systemic artery. Fig. 3 is a drawing of the unit.

METHOD OF PERFUSION

All experiments were performed on adult mongrel dogs of either sex, anesthetized with intravenous pentobarbital, and subjected to total cardiopulmonary by-pass for twenty minutes at normal temperature. After cannulation of the right carotid artery with a No. 14 or 16 F. plastic Bardic oxygen catheter, right thoracotomy was performed in the fourth intercostal space. The pericardium was widely incised, and 1 mg. of heparin per kilogram of body weight was injected into the right atrium. The inferior vena cava and the superior vena cava were cannulated with No. 22 F. plastic catheters via the right auricular appendange and azygos vein, respectively. Twill tapes placed around the cavae were used as tourniquets during the perfusion. A Lucite Y-connector joined the separate caval catheters to the bubble cylinders of the oxygenator by means of Mayon tubing,* 5/16 inch in internal diameter. Gravity drainage was used so that blood in the extracorporeal system traversed the pump only once per cycle. Oxygenated blood was led away from the reservoir and through the filter device in tubing 5/16 inch internal diameter. The pump-to-artery limb of the circuit was bridged with tubing 3/16 inch internal diameter.

Oxygen was introduced into each bubble cylinder at a flow rate of 6 liters per minute since this was found to be the minimal amount of oxygen necessary to saturate 1 liter of venous blood in one minute. Higher oxygen flow rates were used in some experiments, but the bubble size became smaller, and foam was observed to collect in the filter chamber. It became apparent that large bubbles of the same diameter as the paired cylinders were more readily broken by the silicone-coated spheres than were smaller bubbles.

Many of the early experiments were performed with an oxygenator consisting of a single bubble chamber concentrically situated in the reservoir. The safe rate of perfusion with this machine was 1 liter per minute; hence, two bubble cylinders were adopted to permit higher flows. Plastic caps, seen in Fig. 2, were made so that either inner cylinder could be used to the exclusion of the other if flows of less than 1 liter per minute were desired. With both caps in place the reservoir can be used with the pump for by-pass of either the right or left heart.

The extracorporeal system was primed with 750 ml. of heparinized (20 mg. of heparin) venous blood. This was oxygenated by the machine so that no special preparation of the blood was necessary except for its collection in heparin rather than citrate solution. Before total by-pass was instituted with the caval tourniquets, partial by-pass was used to establish an appropriate flow rate for the animal. Failure to maintain a reservoir of 500 to 600 ml. at high flow rates sometimes resulted in transport of foam to the bubble trap. After a minute or two of partial by-pass, total inflow occlusion was effected and the electronic respirator stopped. The by-pass was terminated in reverse order to that of initiation.

The chest was closed after a No. 26 F. rubber catheter had been placed in the right hemithorax. Protamine was given slowly by vein in a dose equal to that of the heparin. Rapid injection of protamine immediately after perfusion often provoked severe depression of blood pressure which in one instance contributed to the onset of ventricular fibrillation. Thereafter, protamine was withheld until the chest was closed and preferably until the dog was off the respirator. The chest tube was frequently aspirated during the first two hours postoperatievly, and the amount of drainage was recorded. No animal was transfused following the procedure.

Blood gas analyses were done before and after perfusion, as were blood pH, plasma hemoglobin, and blood constituent determinations. Platelet counts were followed 90 minutes into the postperfusion period as was the pH. Gas analyses and pH determinations were

*Mayon Plastics, Minneapolis, Minn.

also performed at intervals on blood from the oxygenator. In some experiments abdominal aortic pressures were measured by means of a Statham strain gauge and Sanborn Polyviso recorder.

Fig. 4 is a drawing of the artificial heart-lung system.

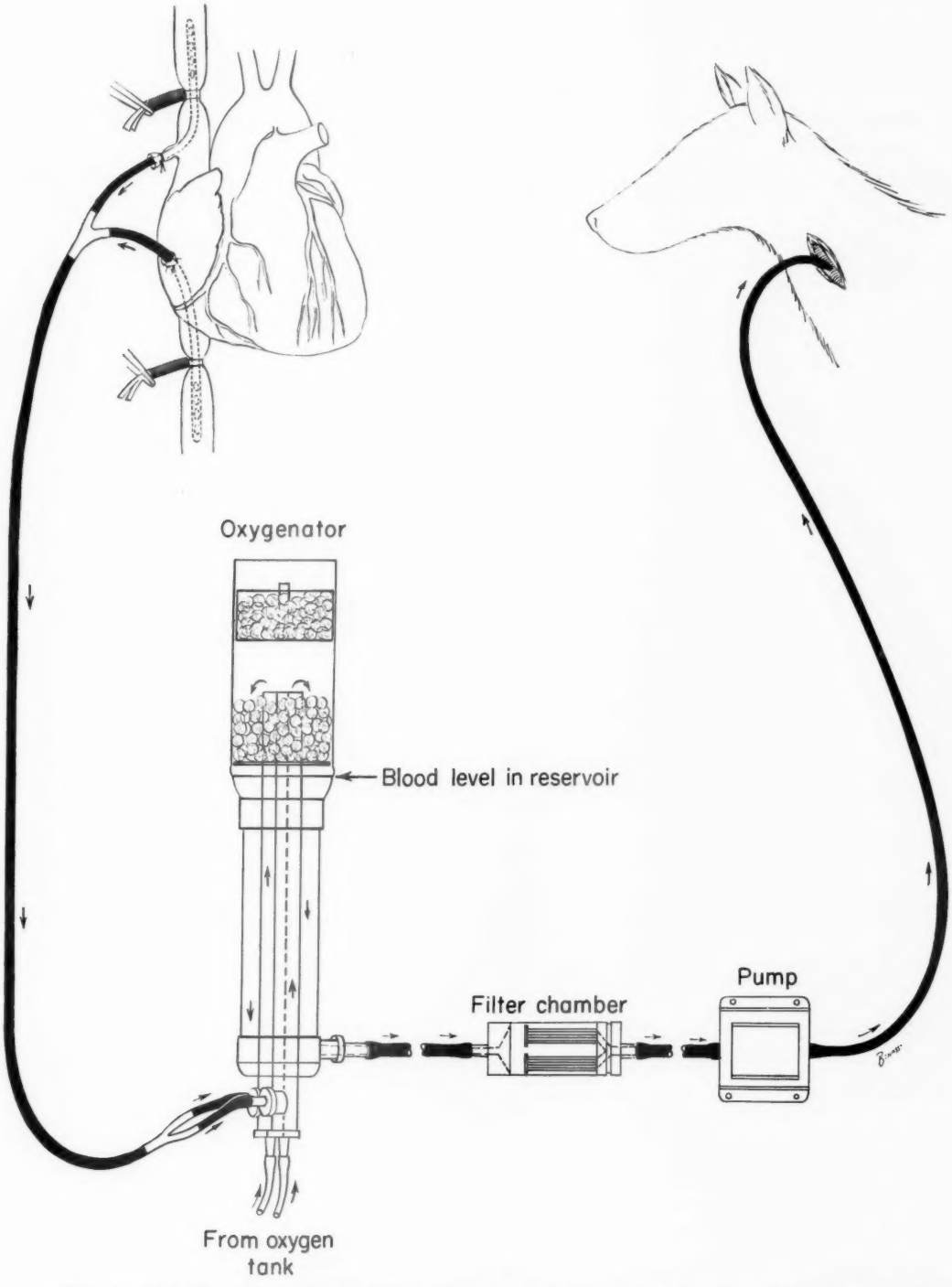

Fig. 4.—Schematic drawing of the oxygenator during perfusion. Blood from the cavae reaches the oxygenator by gravity drainage, passes through the filters, and is then pumped into the carotid artery.

RESULTS

The apparatus was employed in experiments on 26 dogs, with 20 survivors and 6 deaths. The duration of total by-pass, 20 minutes, is a reasonable period of time in which to carry out intracardiac surgery. Most of the deaths came early in the experience before the essentials of the technique were recognized. In the second series, right ventriculotomy was performed on 15 consecutive dogs totally by-passed for 20 minutes, with only two deaths, one from cardiac tamponade and the other from an overdose of anesthesia. There were no mysterious deaths, and no evidence of gas or particulate emboli was detected. Postperfusion bleeding was no problem; the usual amount of drainage aspirated from the chest was 100 ml. Table I is a compilation of the results.

TABLE I. RESULTS WITH MECHANICAL HEART-LUNG SYSTEM

	NUMBER OF DOGS	DURATION OF TOTAL BY-PASS (MINUTES)	SURVIVORS	DEATHS	VENTRICULAR FIBRILLATION	FLOW RANGE (C.C. PER MINUTE)
Preliminary Series (No cardiotomy)	11	20	7	4	0	300 to 1,780
Right Ventriculotomy Series	15	20	13	2	3	310 to 1,000
Total	26	20	20	6	3	300 to 1,780

TABLE II. LABORATORY DATA FROM PROTOCOLS OF 10 CONSECUTIVE DOGS SUBMITTED TO 20 MINUTES OF TOTAL CARDIOPULMONARY BY-PASS WITH SURVIVAL

		PH	CO_2 (VOL. PER CENT)	O_2 (VOL. PER CENT)	PLASMA HEMOGLOBIN (MG. PER CENT)	HEMOGLOBIN (GM. PER CENT)	PLATELETS
Immediately Before Perfusion							
	Mean	7.42	43.15	18.72	25.3	15.0	280,000
	Range	7.26	28.57	14.05	0	10.7	153,000
		7.61	58.82	21.70	72	17.3	446,000
Immediately After Perfusion							
	Mean	7.45	27.15	19.46	107	15.6	97,900
	Range	7.30	17.83	15.39	43	11.7	26,000
		7.68	38.34	23.47	262	18.2	185,000
Machine Sample							
	Mean	7.31	35.73	20.47			
	Range	7.21	29.58	14.79			
		7.47	46.91	23.50			
90 Minutes Postoperative							
	Mean	7.24					187,000
	Range	7.13					74,000
		7.34					283,000

Laboratory data in 10 consecutive experiments are summarized in Table II. The plasma hemoglobin increment did not exceed 100 mg. per cent in the majority of animals. Postoperatively a slight fall in pH was commonly noted, probably heralding a metabolic acidosis in response to subnormal flow rates. The platelet count customarily returned close to the preperfusion level 90 minutes after closure of the chest. In general, adverse physicochemical effects of the oxygenator were of insignificant magnitude. Pressures recorded in the

abdominal aorta varied from 50 to 120 mm. Hg, depending upon how nearly the cardiac output was approached by the rate of perfusion.

Perfusion rates were varied somewhat for animals of the same weight. The rate of perfusion ranged from 30 ml. per Kg. per minute to 75 ml. per Kg. per minute. The usual flow rate was between 40 and 50 ml. per Kg. per minute. Flow rates were estimated at the end of each experiment by diverting blood from the arterial limb of the system into a graduated cylinder for a given period of time. Calculation of flow rate in this manner is likely to contain a systematic error on the high side because of diminution in the resistance against which blood must be pumped. Since the finger pump is relatively insensitive to changes in resistance, the degree of amplification of flow rate must be small.

Venous return to the oxygenator was modified by several factors: individual differences in the dogs, the relative size of the venae cavae and the caval catheters, distance between the heart level and the oxygenator, and the arterial blood pressure. If a fall in blood pressure preceded the by-pass, venous return was substantially diminished probably from peripheral pooling of the blood, and the flow rate consequently was low throughout the perfusion. Partial by-pass instituted as soon as possible after the cavae were cannulated aided in the prevention of this initial drop in blood pressure. Manipulation of the heart and incomplete obstruction of the cavae by their catheters were probably active in precipitating the early blood pressure diminution.

DISCUSSION

The idea of perfusing blood with oxygen is nearly as old as the discovery of oxyhemoglobin. Nonetheless, certain recent advances are directly responsible for the feasibility of bubble oxygenators. Outstanding among them is the evolution of an efficient, nontoxic, antifoam agent. Another item worthy of comment is the use of inert plastics which are less deleterious to blood than is glass. A third factor is derived from the azygos flow concept, promulgated by Andreasen[1, 2] and utilized in cross circulation by Lillehei.[21] The low flow principle no doubt is better suited for cross circulation than for the mechanical heart-lung because buffer systems inherent in the donor technique are notably absent in any artificial unit. The metabolic acidosis of cardiopulmonary by-pass at low flow rates is neutralized instantaneously by the donor, while with the mechanical apparatus a longer period of derangement certainly occurs. The physiologic status of an animal maintained on his own azygos venous return to the heart is very different from that of a dog submitted to total cardiopulmonary shunt. Suffice it to conclude from the work of Andreasen that animals should tolerate perfusion flow rates substantially less than cardiac output for short periods of time, but the expression of perfusion rates in terms of azygos flow is meaningless.

No effort was made to return coronary drainage blood to the oxygenator. At the flow rates employed, the amount of coronary drainage was easily replaced by gravity flow from a bottle reservoir into the afferent side of the oxygenator. The retrieve of coronary drainage has always been a problem in the use of heart-lung machines. Two factors actually combine to obviate the necessity for coronary drainage pickup: a decreased coronary flow in response

to a relatively low perfusion rate, and tolerance of the heart to intermittent aortic occlusion during open cardiotomy as practiced clinically by Lillehei[21] after the experimental work of Wesolowski.[27] These considerations also permit better identification of intracardiac anatomy, the essentials of which can be obscured both by high coronary flows and incompetence of the aortic valve. A further maneuver which would diminish blood loss from the open heart during perfusion is the use of bilateral pulmonary hilar tourniquets. The principal advantage here, of course, would be prevention of blood loss from the bronchial circulation.

Temperature loss was not troublesome; however, rectal temperatures in animals weighing 10 Kg. or less sometimes fell to 32° or 33° C. Concentric position of the bubble cylinders in the reservoir tends to insulate the system and, therefore, minimizes temperature loss. Although there is no convincing evidence that the loss of a few degrees of body heat is deleterious, contemplated expedients for the abolition of any heat loss include hot water immersion of the entire oxygenator and placement of warm blankets under the patient.

It will be noted that ventricular fibrillation occurred in three of the right ventriculotomy group. Each was successfully defibrillated, but the fact that ventricular fibrillation was encountered at all suggests that a sizable series of dogs consecutively submitted to ventriculotomy without fibrillation is unlikely. This is certainly true at temperatures below 30° C., regardless of the protective device invoked.

One further point in the possible clinical application of this system concerns the technique of approach to the repair of interventricular defects. Probably most defects, those of the membranous septum, are readily approached through the tricuspid valve and right atrium. This contention has been previously stated.[20] A possible, even likely, contributing cause for the appreciable mortality associated with repair of ventricular septal defects is violation of the principal pumping chamber of the right heart and necessary division and suture of the papillary muscle of the conus or even of the anterior papillary muscle of the tricuspid valve. Right ventriculotomy should not be done until preliminary intracardiac exploration has been performed either with a finger inserted through the right auricular appendage or under direct vision through a small right atriotomy which can be closed with a clamp and sutured leisurely at the completion of by-pass.

SUMMARY AND CONCLUSIONS

A simple technique is described for the artificial maintenance of cardiorespiratory function with an efficient, carefully machined, gas dispersion oxygenator. The results of consecutive dog experiments are given.

Several technical points are discussed in contemplation of clinical adaptation of the apparatus for closure of interventricular septal defects under direct vision.

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CARDIAC BY-PASS USING AUTOGENOUS LUNG FOR OXYGENATION

With Particular Reference to Open Gravity Drainage of the Pulmonary Venous Return

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THE merits of utilizing an intact lobe of the dog's own lung as an oxygenator during total cardiac by-pass have been described previously.[2] Despite the success of autogenous lobe oxygenation in the experimental animal, this technique was superseded for initial application in man by the use of a donor circulation.[6] Cross circulation was preferred in these ventricular cardiotomies because, at that time, certain technical difficulties in the use of autogenous lungs were anticipated. These problems were: the multiple cannulations required, the need for keeping the lungs inflated throughout the intracardiac procedure thus interfering with surgical exposure, the sudden occurrence of pulmonary edema in the oxygenating lobe should the delicate balance between its inflow and outflow be inadvertently altered, and the possibility that a single lobe of the human lung, especially if already damaged by pulmonary hypertension, might not be sufficient.

Clinical experience[5] with controlled cross circulation in 45 children has clarified most of these anticipated problems. The validity of the low-flow principle[3] has been confirmed. The vital functions of the lung apart from its oxygenating ability have been appreciated. This experience has made the problems related to familiarity with intracardiac anatomy and satisfactory techniques for cannulation of the great vessels less formidable; and, finally, these operations have demonstrated that ventilation of the lungs during cardiotomy probably would not interfere significantly with the reparative surgery. Campbell and associates[1] have shown that the risk of pulmonary edema occurring in perfused lungs is significantly reduced by adopting open drainage of the pulmonary venous outflow. These observations coupled with the significant advantage to be obtained in regard to simplicity, safety, and wide applicability of a method for total cardiac by-pass utilizing the intact lung as an oxygenator have prompted us to re-examine the use of the patient's own lung for open intracardiac surgical procedures. Many of the technical factors associated with the use of autogenous lung during cardiac by-pass

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have been described previously. The present studies were designed to ascertain the best technique for the collection of blood from the left atrium using open gravity drainage to avoid pulmonary edema.

METHODS

Two main types of experiments were performed using the left lung as an oxygenator: total cardiac by-pass; and left heart by-pass.

The dogs used in these studies were subdivided on the basis of the method used for collecting the pulmonary venous drainage: open gravity drainage into the thoracic cavity (Fig. 1); closed gravity drainage of the left atrium (Fig. 2).

All animals were anesthetized with morphine, atropine, and Pentothal sodium. Air under intermittent positive pressure was administered with an endotracheal tube. The left chest was opened through the bed of the fifth rib with the dog in the dorsal position. The left atrium was dissected free from adjacent structures. Cotton tapes were next placed about the venae cavae at their entrance into the right atrium. A similar tape was looped about either the left or right pulmonary artery immediately distal to the bifurcation of the main vessel.

Cannulations.—For total cardiac by-pass the left common carotid, the venae cavae, and the main pulmonary artery were cannulated with No. 14 plastic catheters (Bardic*) as portrayed in Fig. 2. For left heart by-pass the cannula was inserted only into the common carotid and the oxygenated blood was collected in both cases from the left atrium.

Blood Collection.—The blood needed to fill the extracorporeal portion of the circuit and to replace the animal's operative losses was collected on the day of operation from donor animals which received intravenous succinyl choline chloride and locally injected Novocain for anesthesia. The pulmonary venous blood was drained into a cylindrical plastic reservoir which contained 500 c.c. of arterial blood with 18 mg. of heparin.

Pump.—The mechanism† consisted of two heads containing multiple, cam-operated, metal fingers which massaged the blood within ⅜ inch gum rubber tubing in a unidirectional manner. The rate of flow was preset to deliver 30 c.c. per kilogram per minute from the reservoir to the dog. In total cardiac by-pass experiments an equal amount of blood was pumped from the vena caval catheter into the left pulmonary artery.

Cardiac By-Pass Procedure.—Animals were heparinized with 1 mg. per kilogram injected intravenously immediately before cannulation, equivalent amounts of protamine sulfate being given at the end of the experiment. The output of the right ventricle in the left heart by-pass studies was balanced with that of the pump by controlling the venae cavae inflow with tension on the tapes. The venous blood was diverted into the left lung by constricting the right pulmonary artery.

At the end of twenty to thirty minutes of cardiac by-pass, arterial and venous samples were analyzed whenever possible for oxygen content, oxygen capacity, carbon dioxide content, hemoglobin, plasma hemoglobin, platelets, and pH with the use of standard techniques.

Incisions made into the left atrium were sutured and the pulmonary arteriotomy was similarly oversewn. The chests of these dogs were closed with temporary intermittent tube suction. Antibiotics were given and the animals kept for survival.

RESULTS

A total of 85 dogs were studied with particular reference to the technique of collecting the venous blood returning from the left lung.

*C. R. Bard, Inc., Summit, N. J.
†Sigmamotor Inc., Middleport, N. Y.

Open Drainage Into the Chest Through a Left Atriotomy (Fig. 1).—

Without a separating clamp between the entrance of the left pulmonary and mitral valve: In 10 dogs an attempt was made to divert completely the pulmonary venous outflow away from the mitral valve by making a large posterior incision into the left atrium and then draining the left chest into the reservoir with a stainless steel intercostal cannula (Fig. 1).[4] Complete by-pass was obtained as evidenced by left ventriculotomy but air embolism occurred in 6 dogs during the perfusion. Three out of the remaining 4 dogs were long-term survivors.

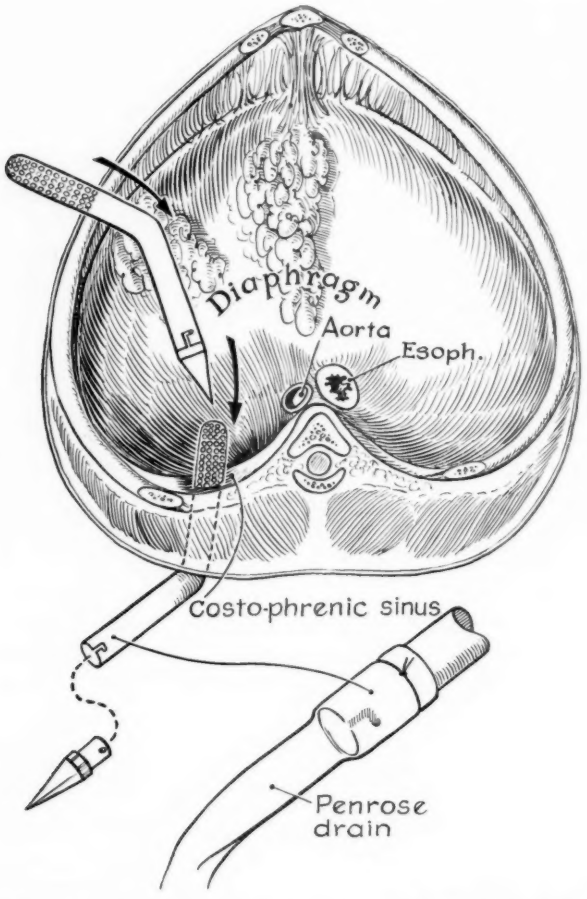

Fig. 1.—Schematic illustration of the open chest drainage technique.

With a separating clamp between the entrance of the left pulmonary and mitral valve: To avoid air embolism a clamp was placed across the atrium so as to separate a left pulmonary venous drainage area. This part of the atrium was drained into the chest with a small dependent incision. Complete cardiac by-pass was achieved in all of 24 animals; 8 subsequently died within the first postoperative week. These deaths were due to overtransfusion, postoperative bleeding, and liver infarction. The last complication may have resulted from inadvertent placement of the inferior vena caval catheter tip into the common hepatic vein.

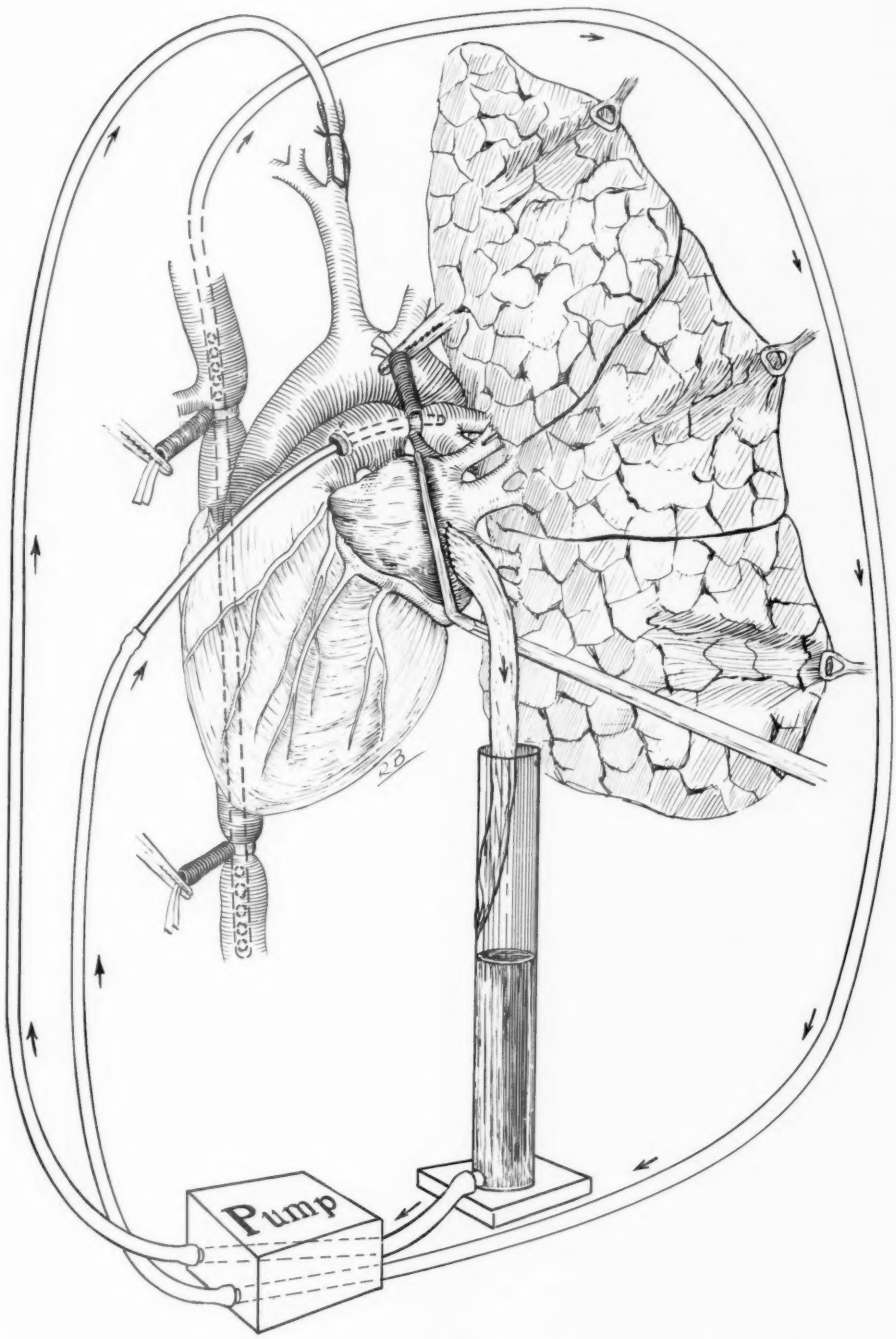

Fig. 2.—A diagrammatic representation of the circuit and cannulations used as a basis for the cardiac by-pass experiments.

Closed Gravity Drainage of the Left Atrium.—

Inlying cannulae: Various sizes of rubber and plastic catheters were introduced into the left atrium or left pulmonary veins of 30 dogs. The auricle was the easiest site of insertion, but because of its eccentric location proved to be the least favorable for good gravity drainage. The small cavity of the atrium made direct placement of cannulae difficult without causing pulmonary edema due to obstruction of the orifice or kinking of the wall. Separate cannulations of the left pulmonary veins were given up as technically not feasible in the dog. Gravity drainage alone was unable to empty the atrium and clamping off of the pulmonary drainage area with inclusion of the auricular appendage was associated with occasional compromise of the closely adjacent left coronary artery. Introduction of the catheters was occasionally followed by air embolism. In only 3 animals was prolonged by-pass of the left heart successfully accomplished by this method.

Penrose drainage of the left atrium: Penrose drains, $\frac{3}{16}$ to $\frac{1}{2}$ inch in diameter were sutured with continuous No. 6-0 silk onto the left pulmonary confluence area of 21 dogs. A right-angled cardiovascular clamp separated this drainage site from the mitral orifice (Fig. 2). Left heart by-pass was successfully accomplished in 9 dogs, in 1 of these using the total cardiac output of 3,200 c.c. per minute. In another dog the output of the pump was temporarily reduced to 12 c.c. per kilogram per minute, resulting in some right heart failure. With flows greater than 20 c.c. per kilogram per minute the output of the right ventricle spontaneously equilibrated after a few minutes with the arterial input from the pump and reservoir. Two animals died postoperatively, one of pneumothorax and the other from pneumonia at 72 hours.

Complete cardiac by-pass was undertaken in 12 other animals. The left pulmonary artery catheter was originally inserted through the outflow tract of the right ventricle. This caused ventricular fibrillation in one animal. Later cannulations were performed through the main vessel. The best site for placement of the atrial Penrose drain was found to be inferior laterally at the junction of the pulmonary veins and left atrium allowing the tubing to hang out of the incision without kinking. Three of the dogs in which total by-pass was used died in the first week postoperatively.

Metabolic Studies.—The results of metabolic studies made on 22 of the open chest drainage animals and 7 of the Penrose tubing perfusion experiments are shown in Fig. 3. Both groups illustrate the efficient oxygenation of the perfused blood by the single lung. The relatively high levels of venous oxygen saturation confirm the fact that the reduced flow was sufficient for these animals which is also stressed by the relatively moderate acidosis developing during the by-pass interval. In comparison with those in which the blood was collected by closed methods, the open chest drainage dogs fared worse from a point of view of blood damage as demonstrated by a higher plasma hemoglobin. Also, the pulmonary ventilation was less efficient as shown by a lower arterial oxygen content, venous content, and pH.

COMMENT

The principal problem in making use of the animal's own lungs during exclusion of the heart has been the satisfactory collection of pulmonary venous outflow. Obviously, the oxygenating capacity of one lung is sufficient for short periods of time. This fact simplifies the technical problems involved. The left lung is preferable because its venous orifices are more accessible and their anatomy (in the human) is more constant. In dogs these veins are so numerous that their separate intubation is practically impossible. To provide a

Determinations	Open Chest Drainage Mean Values 22 Studies	Penrose Drainage Mean Values 7 Studies
Hgb. gms.%	15.9	16.1
O_2 vols.%	art. 19.7 ven. 7.4	art. 20.7 ven. 9.1
CO_2 mM/l.	art. 17.8 ven. 20.5	art. 18.4 ven. 20.2
O_2 cap. vols.%	21.6	22.0
Hgb. sat.%	art. 91	art. 94
pH.	7.25	7.33
pl Hgb. mgm.%	81	32
Platelets cu. mm.	165,000	125,000

Fig. 3.—Metabolic changes following twenty to thirty minutes of cardiac by-pass using autogenous lung for oxygenation and perfusing approximately 30 c.c. per kilogram per minute. Two different methods of pulmonary venous drainage were studied.

dry intracardiac field the oxygenated blood must be diverted before it reaches the mitral valve. The preceding studies have shown that gravity drainage alone cannot empty the left atrium without accompanying air embolism. The confluence area of the left pulmonary veins must be physically separated from the mitral orifice by a clamp or some other means. This collecting chamber can then be drained in several ways. Inlying catheters uniformly produced some obstruction with resulting pulmonary edema and therefore were deemed unsatisfactory. Open external drainage into the chest allowed successful cardiac by-pass without this risk. However, soft rubber drains sutured externally to the atrium had some advantages over drainage through the chest. This latter technique caused more damage to the blood and the blood became sequestrated in the other chest cavity reducing venous return and necessitating a greater blood replacement. Ventilation of the lungs was not as ade-

quate either, as part of the chest cavity was taken up with blood. Penrose drains had the valuable attribute of collapsing, thus avoiding air aspiration with embolism and similarly not allowing intense siphoning effects to develop. This latter technique has proved to be the most satisfactory method of those studied for the collection of pulmonary venous drainage during cardiac by-pass without the risk of pulmonary edema.

SUMMARY

A series of 85 dogs have been operated on to establish a satisfactory technique for collection of pulmonary venous outflow during cardiac by-pass with the use of the left lung as an oxygenator.

Diversion of blood from the mitral orifice depended upon physical separation of the venous confluence area with a nonerushing clamp.

Gravity drainage of this collecting chamber was best accomplished with externally sutured Penrose drains. This technique eliminated the problem of pulmonary edema.

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EFFECT OF BASILAR CARDIAC DENERVATION AND CARDIOPNEUMONOPEXY ON VENTRICULAR FIBRILLATION AFTER ACUTE CORONARY OCCLUSION

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THE exact mechanism by which ventricular fibrillation is initiated spontaneously after coronary occlusion is unknown. Wiggers[23] found that when an electric current is applied to the heart, ventricular fibrillation is induced only when the stimulus is strong enough and a portion of it is applied during the last 0.05 to 0.06 second of systole. In ventricular fibrillation occuring spontaneously after acute coronary occlusion, it is postulated that an ectopic stimulus arising in the heart probably falls within the vulnerable period of systole "triggering" fibrillation. Harris and Rojas[11] report that acute myocardial ischemia greatly reduces the fibrillation threshold of the ventricle and a natural electrical impulse, if discharged at the proper moment, is sufficient to fibrillate the ventricles. Beck[3] proposed the concept of an irritable focus developing in the ischemic area of the myocardium after acute infarction to "trigger" ventricular fibrillation. His experiments further demonstrated that when a small amount of blood is delivered to this ischemic myocardium, fibrillation and death are prevented.

A hypothesis of reflex coronary vasoconstriction has been advanced as an explanation of sudden cardiac death from coronary occlusion.[13] The stimulus to fatal ventricular fibrillation is the ischemic myocardium, whose afferent path is the cardiosensory innervation and whose efferent path is the vagus. In support of this view the mortality rate from ligation of a coronary artery has been found to be greater in unanesthetized dogs than in anesthetized animals,[15] and certain drugs will decrease the mortality rate in dogs.[14] Fauteux[8] discovered that pericoronary neurectomy could prevent ventricular fibrillation appearing after sudden coronary occlusion. He used an Adrenalin test to produce tachycardia and incite fibrillation. All animals in an unprotected control group developed ventricular fibrillation in one or two minutes, while those protected by pericoronary neurectomy all survived.

A study of the contractibility of ischemic myocardium reveals that within three to four seconds after the anterior descending branch of the left coronary artery is ligated, a segment of the myocardium at the apex of the heart ceases to contract.[18, 20] This phenomenon of noncontractibility of the ischemic muscle results in "ballooning" of this area during systole. If the area of "ballooning" is of sufficient size, the left ventricular output is diminished, coronary blood flow reduced, and ventricular fibrillation soon results. Murry[16] investigated the effects of the splinting action of a piece of

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cloth sutured over an area of myocardium to be infarcted. The cloth limited myocardial bulging, reducing the amount of blood pressure drop and the fall in cardiac output observed in control animals. He also demonstrated that resection of the infarcted area of myocardium resulted in a survival rate of 80 per cent and that the cardiac output increased. Allen[1] successfully used strips of fascia or pericardium woven through the ischemic muscle to prevent "ballooning" and ventricular fibrillation after coronary artery ligation.

An experimental operation has been designed to counteract some of these adverse factors which are known to influence ventricular fibrillation after acute coronary occlusion. Basilar cardiac neurectomy was selected to determine its effect on the ventricular fibrillation threshold. The splinting effect of cardiopneumonopexy to prevent "ballooning" of the ischemic myocardium was studied and a combination of the two procedures was used to compare the ventricular fibrillation rate, death rate, and the degree of protection of the myocardium after ligation of the left anterior descending coronary artery.

EXPERIMENTAL STUDIES

Experiment I: Ventricular Fibrillation After Ligation of the Anterior Descending Branch of the Left Coronary Artery.—Mongrel dogs weighing 25 to 50 pounds are anesthetized with intravenous Nembutal sodium (veterinarian), 1 gr. per 5 pounds weight. An intratracheal tube is inserted and positive pressure air administered by an anesthetist. The animal is placed on its back, tilted slightly to the right with the left side up. The skin is prepared with 10 per cent tincture of iodine and 70 per cent alcohol. An 12 cm. incision is made in the fourth intercostal space, the fourth and fifth costal cartilages incised, and a small Finochietto retractor inserted to obtain exposure. The pericardium is opened exposing the heart. The left auricle is retracted laterally to expose the origin of the left coronary artery. At a point 3 to 5 mm. distal to bifurcation of the circumflex branch, the anterior descending coronary artery is doubly ligated and divided. The wound is closed with the lungs inflated and all residual air aspirated through an 18 gauge needle. All animals were given 600,000 units of procaine penicillin prior to surgery. Electrocardiographic tracings are made prior to and at the time of ligation, and the time of onset of fibrillation is recorded.

Twenty mongrel dogs were used. Ventricular fibrillation and death occurred within twenty-five minutes after ligation in eleven animals and within thirty minutes in 2 dogs. Two dogs lived twelve and eighteen hours, respectively, after ligation and died as a result of acute infarction with myocardial failure (Fig. 1). The surviving animals in this control series all gave electrocardiographic evidence of acute myocardial infarction. These animals were sacrificed one to three months after operation and all were found to have large anterior apical infarcts averaging 4 by 3.5 cm. in diameter.

After ligation of the anterior descending branch of the left coronary artery at its origin careful observation revealed almost immediate loss of contractibility of the ischemic myocardium (within five seconds). Cyanosis of the ischemic muscle was visible after thirty to forty seconds. "Ballooning"

of the infarcted muscle could be seen during systole. As the ventricular output decreased, marked cyanosis of the involved myocardium occurred and ventricular fibrillation soon followed.

Tachysystole occurred prior to the onset of ventricular fibrillation, lasting one or two seconds. This was followed by convulsive myocardial incoordination which progressed to atony of the myocardium.

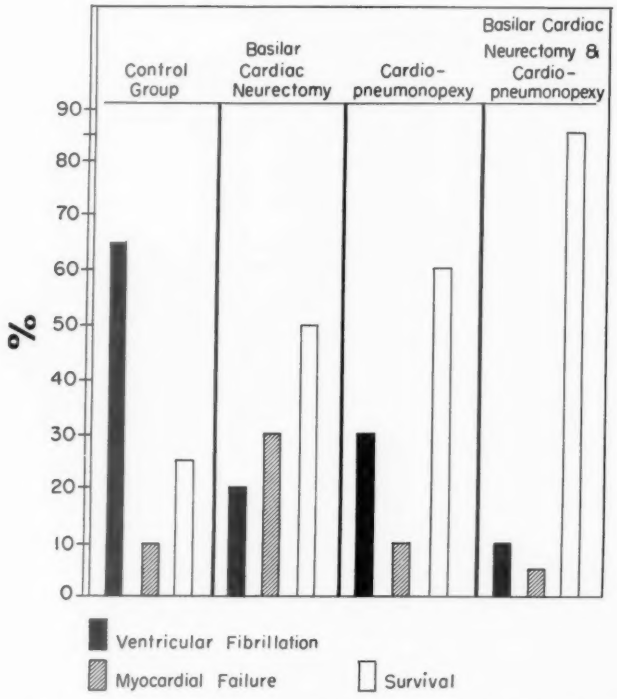

Fig. 1.—Result of ligation of anterior descending branch of left coronary artery.

Experiment II: Technique of Basilar Cardiac Neurectomy and Its Effect on Ventricular Fibrillation After Ligation of the Anterior Descending Branch of the Left Coronary Artery.—After opening the left pleural space as previously described, the pericardium is opened 1 cm. anterior to the left phrenic nerve exposing the aorta. The preaortic fat pad is excised, and the adventitia at the base of the aorta removed over a 5 cm. area circumferentially, interrupting the periaortic sympathetic and parasympathetic nerve fibers (Fig. 2). Dissection is continued along the arch of the aorta to sever the cardiac branches of the vagi and the sympathetic cardiac fibers. The cardiac plexus of nerves between the arch of the aorta and the pulmonary artery is excised. Retracting the pulmonary artery downward and to the left, the dissection is continued beneath the aorta, interrupting the cardiac nerves that cross the right pulmonary artery to the origin of the coronary arteries. The few remaining cardiac nerve fibers over the base of the main pulmonary artery and the left pulmonary artery are interrupted.

The left auricle is retracted laterally and two No. 2-0 silk ligatures are placed around the anterior descending branch of the left coronary artery 3 and 5 mm. distal to its junction with the circumflex branch. The ends of

these ligatures are left long for subsequent coronary ligation. Pericardium over the base of the heart is closed with a continuous No. 4-0 silk suture and the chest closed as in the previous experiment.

Twenty to 100 days after basilar cardiac denervation the previous thoracotomy incision is again opened and the two ligatures previously placed about the anterior descending branch of the coronary artery at its origin are tied and the vessel divided.

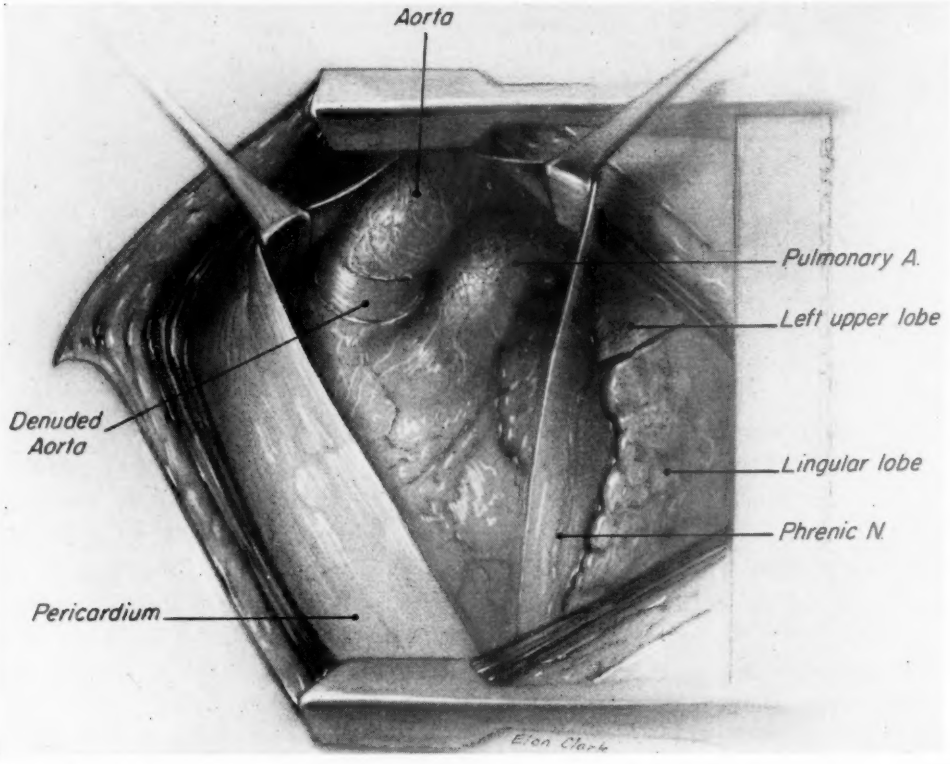

Fig. 2.—Basilar cardiac neurectomy. Adventitia dissected from the aorta circumferentially. Dissection continues along aortic arch severing the cardiac sympathetic and parasympathetic nerve fibers.

Basilar cardiac neurectomy was performed on 10 dogs. Ventricular fibrillation occurred in 2 animals after ligation of the left descending coronary artery. It is noteworthy that the onset of fibrillation was delayed as compared with the control group. In one animal fibrillation started twenty-eight minutes after ligation and in the second at thirty-five minutes. Death occurred at fifty-two and sixty minutes, respectively. Three other animals died of acute myocardial failure within thirty-six to seventy-two hours after ligation. The 5 remaining animals survived and each was found to have a large anterior apical infarct which averaged 4 by 3 cm. in diameter.

Pulse rate increased an average of 15 to 20 beats per minute and remained elevated for the first seventy-two hours postoperatively. Heart rate then gradually returned to normal.

Experiment III: Effect of Myocardial Splinting by Cardiopneumonopexy in Prevention of Ventricular Fibrillation.—Left thoracotomy is performed as

described in the control series. The phrenic nerve is mobilized and retracted laterally. Pericardium is opened from the auricular appendage to the apex of the heart inferiorly. Two ligatures are placed about the left anterior descending branch of the coronary artery 3 to 5 mm. from its junction with the left circumflex branch. These sutures of No. 0 silk are left long for subsequent ligation at the second operation. Interrupted mattress sutures are placed in the medial edge of the middle lobe of the left lung and passed

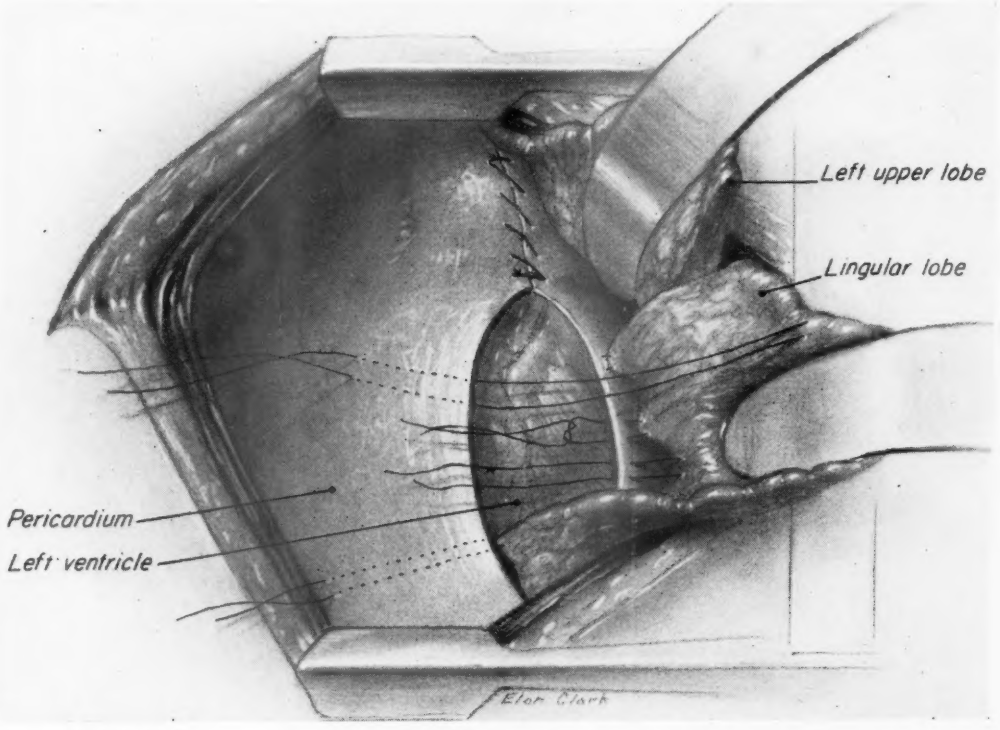

Fig. 3.—Cardiopneumonopexy. Interrupted mattress sutures are placed through the pericardium and lung so that when tied the lung is placed over the left ventricle and apex of the heart. Asbestos powder is applied to the epicardium and lung before the sutures are secured.

through the pericardium so that, when tied, the lung is drawn into position over the left ventricle and apex of the heart (Fig. 3). Sterile asbestos powder (0.2 Gm.) is applied to the epicardial surface of the heart and the undersurface of the middle lobe. The mattress sutures are secured, sliding the lung into the pericardial cavity to cover the apex and left ventricle. Several interrupted fine silk sutures approximate the open pericardial edge to the anterior surface of the middle lobe, closing the pericardial space and preventing the escape of asbestos powder into the pleural cavity. The left pleural cavity is closed as previously described.

Fourteen to twenty-one days following cardiopneumonopexy the left pleural cavity is reopened and the sutures which had been placed about the left anterior descending coronary artery at its origin are tied and the artery sectioned.

Ten animals were used in this experiment and the onset of ventricular fibrillation occurred in three at six, ten, and twenty-five minutes after ligation. Two other animals died within thirty-six hours after ligation and 5 survived.

Necropsy studies revealed myocardial infarction in each animal. Average size of infarcts was 3.5 by 3 cm. The autopsy findings showed less myocardial destruction in the animals of Experiment III than in the animals of Experiments I and II. Serial sections through the infarcts of Experiment III animals revealed protection to the muscle on the epicardial side. In no case was there full-thickness necrosis of the myocardium; whereas, in Experiment I, this occurred in 3 animals and in 2 animals in Experiment II.

Experiment IV: *Effect of Basilar Cardiac Neurectomy and Cardiopneumonopexy on Ventricular Fibrillation and Survival After Ligation of Anterior Descending Branch of the Left Coronary Artery.*—The left pleural cavity

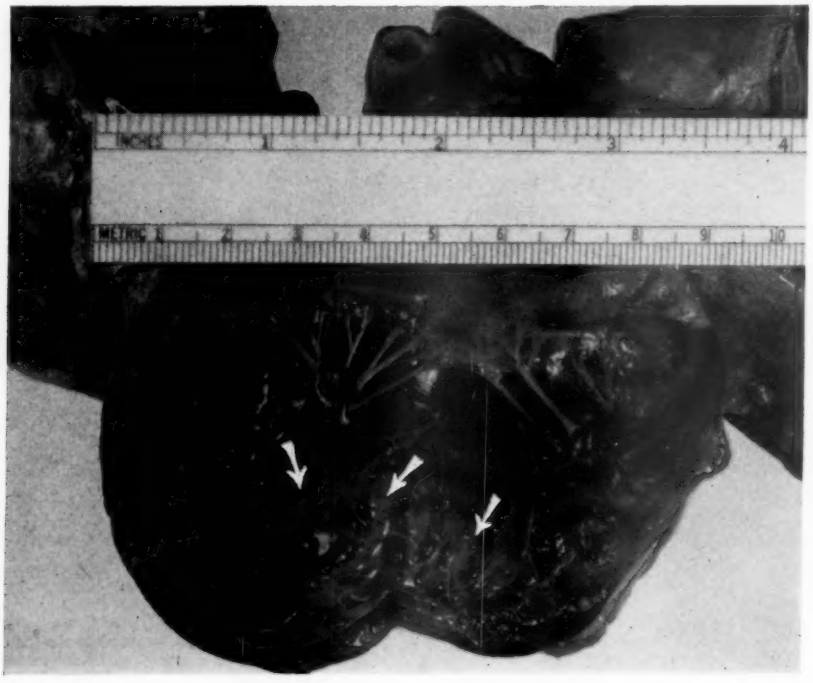

Fig. 4.—Large anterior apical left ventricular infarct measuring 4.5 by 3 cm. which this dog survived. Animal was protected by basilar cardiac neurectomy and cardiopneumonopexy prior to ligation of the left anterior descending branch of the coronary artery. Sacrificed five weeks after ligation.

is opened and a basilar cardiac neurectomy followed by cardiopneumonopexy is performed as described previously. Two ligatures of No. 2-0 black silk are placed about the left anterior descending coronary artery 3 to 5 mm. from the circumflex branch. After the chest is closed, a period of fourteen to one hundred twenty days is allowed to elapse before re-exploration, ligation, and division of the artery.

Of twenty dogs prepared by basilar neurectomy and cardiopneumonopexy, 85 per cent survived ligation of the left anterior descending coronary artery. Ventricular fibrillation and death occurred in 2 animals (75 and 120 minutes after ligation). One dog died of myocardial failure forty-eight hours after ligation. Two animals were followed for two years prior to sacrifice in order to study the effect of partial confinement of the lung within the pericardium. Microscopic examination revealed no evidence of chronic

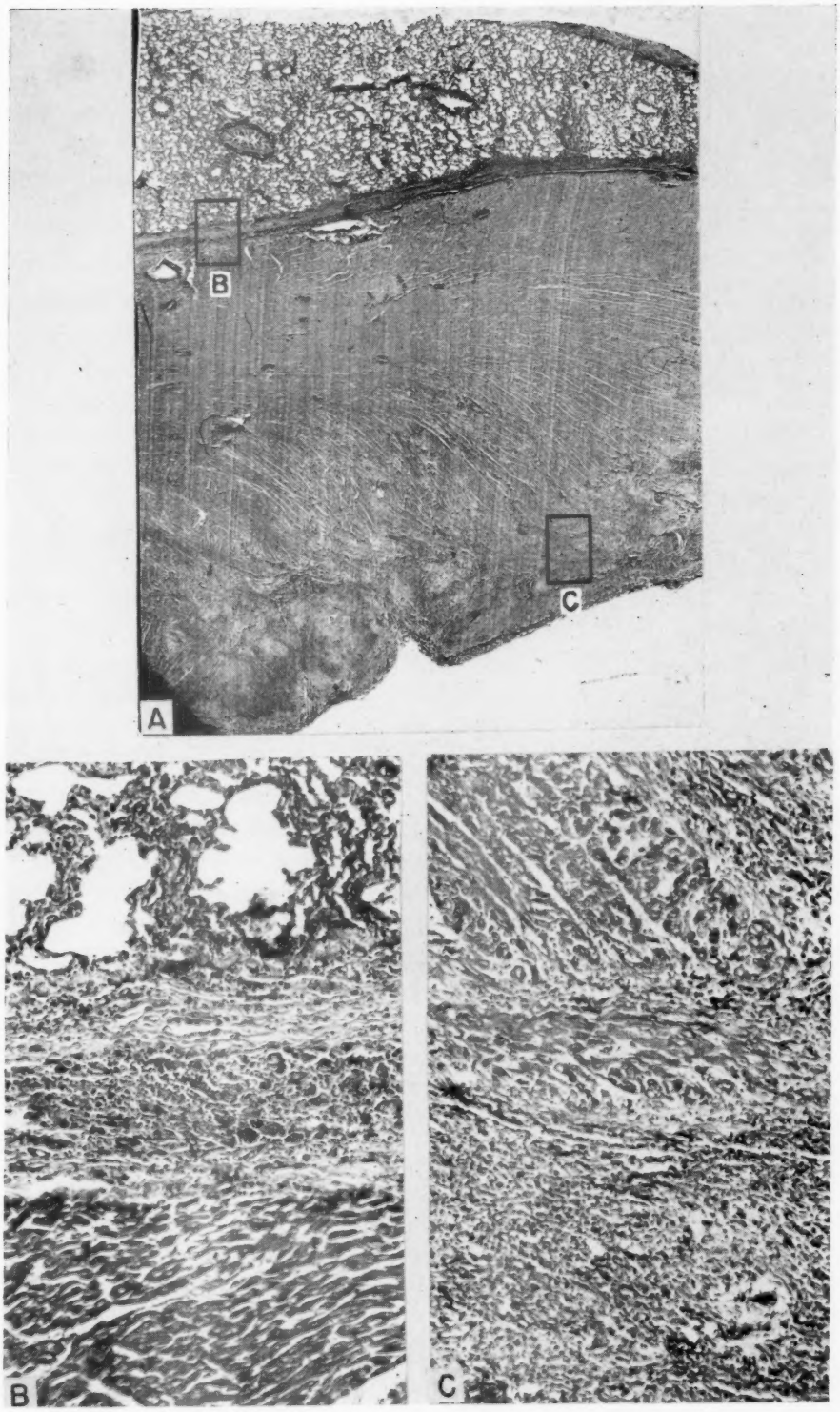

Fig. 5.—*A*, Cross section through the infarcted myocardium of the left ventricle of the heart shown in Fig. 3. Normal myocardium in the subepicardial area protected by adherent lung. The infarcted subendocardial myocardium has been invaded by darker staining inflammatory cells. (×8.5; reduced ⅙.)

B, Photomicrograph from area *B* as shown in *A*. Vascular foreign body granulomatous reaction produced by asbestos powder unites the lung above and the myocardium below. (×122; reduced ⅙.)

C, Photomicrograph from area *C* shown in *A*. Infarcted area of myocardium with replacement of myocardial bundles by polymorphonuclear leukocytes, lymphocytes, and mesenchymal cells. (×122; reduced ⅙.)

infection or bronchiectasis in the confined pulmonary tissue in these 2 animals. The average myocardial infarct measured 2.5 by 2.5 cm. in Experiment IV animals. The largest infarct measured 4.5 by 3.0 cm., yet the dog survived (Fig. 4). Microscopic studies of the infarcts also revealed less myocardial destruction than in the other groups (Fig. 5).

DISCUSSION

Results of these experiments indicate that there is a relationship between the frequency of ventricular fibrillation following acute coronary occlusion in the unprotected control animal and in those protected by basilar cardiac neurectomy, cardiopneumonopexy, or a combination of the two procedures (Fig. 1). The survival rate following ligation of the anterior descending branch of the left coronary artery is increased following these preparatory operations, and the degree of myocardial damage lessened.

Cardiac denervation is of value in relieving pain of coronary origin[2, 6, 8] and stimulating the development of collateral circulation at the base of the heart. Theoretically it is of value in producing coronary vasodilatation[13, 15] and increasing the threshold of ventricular fibrillation to sudden myocardial ischemia. Ventricular fibrillation occured in only 20 per cent of the denervated animals in this experiment compared with 65 per cent of the control animals after acute coronary artery ligation. The question arises as to whether relief of the anginal pain would be detrimental to the patient with coronary artery disease, since it would abolish the warning signal of pain! Fauteux[8] reported that following pericoronary neurectomy his patients developed a sensation of tightness or substernal pressure when they overtaxed their hearts. White[22] noticed similar warning signs in his patients after removal of the upper three thoracic sympathetic ganglia.

The location of myocardial cyanosis and "ballooning" was noted after ligation of the anterior descending branch of the left coronary artery in the control group of animals. This occured at the anterior left ventricular apex of the heart (Fig. 4). In order to determine the value of the splinting effect of the lung, it was placed over this area and adhesions between the heart and lung were produced by the application of asbestos powder. Only 30 per cent of the animals developed ventricular fibrillation after cardiopneumonopexy compared with 65 per cent of the unprotected control animals. The survival rate was 60 per cent after cardiopneumonopexy and 25 per cent in the control group. These figures for survival rate after cardiopneumonopexy are somewhat lower than the 78.9 per cent reported by Carter.[7] This difference is explained perhaps by the use of room air as oxygen supply during anesthesia and the earlier ligation (fourteen to twenty-one days) of the coronary artery before maximum stimulation of intracardiac collaterals and development of extracardiac blood supply. The presence of such extracardiac collateral development from the lung was demonstrated by Carter[7] with India ink injections.

Myocardial infarction is confined almost exclusively to some portion of the left ventricle or the intraventricular septum. The right ventricle is rarely involved. Wartman[21] found only 4 instances in 160 cases of myocardial

infarction. For this reason the left ventricle was selected for experimental protection. It is interesting that in the necropsy specimens the cardiopulmonary adhesions were precisely over the left ventricle only. The right side of the heart remained free of adhesions.

Cardiopneumonopexy acts as a splint preventing paroxysmal myocardial "ballooning" after acute infarction. Of the 20 control animals 2 developed ventricular aneurysms following ligation of the anterior descending branch of the left coronary artery. In 30 animals the infarcted myocardium was protected by cardiopneumonopexy and no aneurysm developed. The importance of this protective mechanism is apparent as clinical statistics reveal that following acute myocardial infarction ventricular aneurysm formation occurs in approximately 9 per cent of cases[17] and myocardial rupture in 10 per cent.[9]

The importance of slow coronary artery occlusion in permitting the development of collateral circulation was demonstrated by Gregg,[10] who produced gradual but complete obliteration of the coronary artery without myocardial infarction. Burchell[5] was able to occlude all three main coronary arteries in dogs by gradually constricting them with metal collars anchored to the chest wall. No infarcts developed. In human instances of coronary arteriosclerosis, coronary artery occlusions are observed without infarctions due to the development of adequate collateral circulation during the period of coronary narrowing.[19] Blumgart,[4] through injection studies on human hearts, reported interarterial anastomosis in 98 per cent of hearts whose vessels were occluded. Given time, the heart is capable of developing sufficient intracardiac collateral circulation to maintain life. Indeed, complete occlusion of both human coronary arteries with survival has been reported and proved by autopsy studies.[12] A surgical operation for coronary artery insufficiency must prevent mechanism death (ventricular fibrillation) to allow the heart time to develop intracardiac collateral circulation.

Sensory disturbances, vasomotor reactions, and mechanical factors affect coronary blood flow after acute coronary occlusion. By combining basilar cardiac neurectomy and cardiopneumonopexy, an attack is made on all of these factors which affect blood flow in this acute emergency. This experimental operation is designed for the patient with angina pectoris to relieve the immediate symptoms of pain and to provide maximum protection from subsequent coronary occlusion. Since ventricular fibrillation is responsible for the majority of deaths following coronary thrombosis, a combination of basilar cardiac neurectomy and cardiopneumonopexy would theoretically offer protection by stimulating the production of intracardiac collateral circulation, splinting the myocardium, increasing the ventricular fibrillation threshold, and providing extracardiac circulation during the emergency.

SUMMARY

1. An experimental study of the effect of basilar cardiac denervation, cardiopneumonopexy, and a combination of the two procedures indicates that the ventricular fibrillation threshold is increased, mortality rate is lowered, and less extensive myocardial infarction occurs following ligation of the anterior descending branch of the left coronary artery.

2. Ventricular fibrillation occurred in 65 per cent of the control animals after acute coronary occlusion but in only 20 per cent of the dogs protected by basilar cardiac neurectomy. After cardiopneumonopexy 30 per cent developed ventricular fibrillation, and by combining basilar cardiac neurectomy and cardiopneumonopexy, only 10 per cent of 20 animals developed ventricular fibrillation.

3. The survival rate in the animals protected by basilar cardiac neurectomy and cardiopneumonopexy was 85 per cent, while in the control group of animals it was 25 per cent after ligation of the left anterior descending branch of the coronary artery.

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EARLY RESULTS OF LUMBAR SYMPATHECTOMY FOR PERIPHERAL OBLITERATIVE ARTERIOSCLEROSIS

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THE purpose of this report is to present the early results of lumbar sympathectomy for arteriosclerotic obliteration at different levels in the arteries of the lower limbs. This is currently of particular importance in view of the recent communications presenting the results of arterial resection or thromboendarterectomy for arterial obstruction above the knee. Although many articles[1, 2, 3, 4, 5, 6, 8, 9] have dealt with the role of sympathectomy for arteriosclerosis of the lower limbs, the results have not been uniformly correlated with the level of obstruction to blood flow. The present series is small; however, it is felt that it will contribute to the evaluation of the over-all problem when combined with other series adopting a similar approach.

METHOD OF STUDY

All of the patients who had received a lumbar sympathectomy for obliterative arteriosclerosis at the Veterans Administration Hospital, Providence, Rhode Island, from November, 1950, to November, 1954, were requested to return to the hospital for study. Sympathectomy had been performed in those cases with severe arterial insufficiency demonstrating some degree of vasomotor activity as evidenced by the clinical findings and the response to the Landis-Gibbons test or to paravertebral Novocain sympathetic block.

A review of the preoperative signs and symptoms was made and compared with the postoperative findings. Careful attention was given to the status of the peripheral pulses, collateral circulation (blanching, flushing, and venous filling times), tissue nutrition, the presence or absence of ulcers, impending or frank gangrene, digital hair, and the measuring of claudication distance.

Each sympathectomized limb was classified according to the method of Robertson and Smithwick[7] on the basis of the preoperative arterial pulsations. In this classification there are four limb types. Type I limbs have all of the peripheral pulses present, including the dorsalis pedis and posterior tibial pulsations. Some pulses are distinctly diminished, and some of these limbs show evidence of arterial calcification on x-ray films. Type II limbs have one or more absent pulses below the popliteal artery. Type III limbs have no pulsating arteries below the femorals, and Type IV limbs have no arterial pulsations below the common iliacs. The effect of lumbar sympathectomy on intermittent claudication, rest pain, and ulceration or gangrene in each limb type was determined.

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RESULTS

Forty-three male patients had received lumbar sympathectomy for obliterative arteriosclerosis. There was one operative death due to acute myocardial infarction. Four patients subsequently died from causes unrelated to their peripheral vascular disease. Three patients could not be traced.

Thirty-five patients returned to the hospital; 14 were three to twelve months, and 21 were one to five years, postoperative. The ages ranged from 33 to 75, with an average of 57.2 years. Twenty-nine patients (82.9 per cent) were in the fifth, sixth, and seventh decades (Table I). Nine patients (20.9 per cent) had diabetes mellitus. Forty-nine lumbar sympathectomies were performed. Fourteen patients received bilateral operations.

TABLE I

Total number of patients	35
Lumbar sympathectomies	49
Diabetes mellitus	9
Age distribution (decades)	
Third	3
Fourth	3
Fifth	13
Sixth	14
Seventh	2
Average age	57.2

Lumbar sympathectomy in most cases was performed through an anterolateral retroperitoneal approach. Routinely, the second and third lumbar ganglia were excised; however, in eight operative reports the anatomic description of the removal of a ganglion at the crus of the diaphragm may be indicative of excision of the first lumbar ganglion as well.

Based on the preoperative pulse findings, eight of the 49 sympathectomized limbs were Type I, 14 were Type II, 23 were Type III, and four were Type IV (Table II). Thus, 27 limbs (55.1 per cent) had no pulsations below the femoral artery.

TABLE II. PULSE CATEGORIES (PREOPERATIVE)

TYPE	NO. OF LIMBS
I	8 (16.3%)
II	14 (28.6%)
III	23 (46.9%)
IV	4 (8.2%)
Total	49 (100%)

Intermittent Claudication.—Thirty-five sympathectomies were performed on 28 patients who had complained of severe intermittent claudication (Table

TABLE III. INTERMITTENT CLAUDICATION (RESULTS)

TYPE	NUMBER OF LIMBS	IMPROVED	UNIMPROVED	WORSE OR AMPUTATED
I	3	3	0	0
II	9	5	2	2
III	19	9	5	5
IV	4	1	3	0
Total	35	18 (51.4%)	10 (28.6%)	7 (20.0%)

III). Walking, preoperatively, was limited to less than one city block in sixteen limbs, one block in seven limbs, two blocks in six limbs, three blocks in five limbs, and four blocks in one limb. Twelve limbs were Types I and II, and 23 limbs were Types III and IV. The postoperative claudication distance was measured in a hospital corridor, walking at the rate of 120 steps per minute. The distance walked at the onset of calf pain correlated remarkably well with the postoperative subjective impression. To be considered improved the patient was required to walk at least twice the distance tolerated preoperatively without symptoms.

Of the 35 limbs, 18 (51.4 per cent) were definitely improved. Ten limbs (28.6 per cent) showed no improvement by the criteria previously mentioned, although in some there was a subjective decrease in severity of symptoms and the period of rest required for the relief of pain was measurably shortened. Seven limbs (20.0 per cent) became worse or required an amputation. Of the 23 Type III and IV limbs, 10 (43.5 per cent) were improved, 8 (34.8 per cent) were unimproved, and 5 (21.7 per cent) became worse or required an amputation (Table IV).

TABLE IV. INTERMITTENT CLAUDICATION (PULSES ABSENT BELOW FEMORAL)

TYPE	NUMBER OF LIMBS	IMPROVED	UNIMPROVED	WORSE OR AMPUTATED
III	19	9	5	5
IV	4	1	3	0
Total	23	10 (43.5%)	8 (34.8%)	5 (21.7%)

Rest Pain.—Thirteen patients experienced rest pain preoperatively, primarily in limbs with marked degrees of atrophy or ulceration. Of the 15 limbs in this group, complete relief of rest pain occurred in 5 limbs, no relief was obtained in 2 limbs, 4 required a minor amputation, and 4 major amputations were performed (Table V). In the 11 Type III and IV limbs, only 4 (36.7 per cent) obtained relief by sympathectomy alone. However, when local amputation of ulcerated digits or a transmetatarsal amputation was performed in 3 more Type III limbs, a total of 7 (63.6 per cent) were salvaged and free of pain.

TABLE V. REST PAIN (RESULTS)

TYPE	NUMBER OF LIMBS	RELIEVED	IMPROVED WITH LOCAL AMPUTATION	NO CHANGE	WORSE OR MAJOR AMPUTATION
I and II	4	1	1	1	1
III and IV	11	4	3	1	3
Total	15	5	4	2	4

Ulceration or Gangrene.—Ulceration was present in 23 limbs preoperatively. Ulcers extending to bone or involving tendons did not heal. Of the total group, 10 healed, 3 persisted, 4 required a minor amputation, and 6 a major amputation (Table VI). There were 15 Type III and IV limbs with preoperative ulceration. Seven ulcerated limbs healed, although 2 required minor amputations in addition; 3 persisted, and 5 required major amputations.

TABLE VI. ULCERS AND GANGRENE (RESULTS)

	TYPE	NO. OF LIMBS	HEALED	MINOR AMPUTATION	NO CHANGE	MAJOR AMPUTATION
Ulcer	I and II	8	5	2	0	1
	III and IV	15	5	2	3	5
	Total	23	10	4	3	6
Gangrene	I and II	5	1	2	1	1
	III and IV	8	0	3	0	5
	Total	13	1	5	1	6

There were 13 limbs with gangrenous changes prior to sympathectomy. In one limb the gangrenous area ulcerated and eventually healed, while in another limb it persisted unchanged. Minor amputations were performed in 5 limbs, and 6 major amputations were required. Of the right Type III and IV extremities with preoperative gangrenous changes, 3 resulted in minor and 5 in major amputations.

Major Amputations.—Major amputation in this series is defined as amputation above the ankle. There were 6 major amputations in the total group of 49 limbs, an incidence of 12.2 per cent. Five amputations were performed on Type III and IV extremities, an incidence of 18.5 per cent in the group of sympathectomized limbs with absent pulses below the femoral artery. Two of these amputations were performed within three months postoperatively on limbs which probably could not have been totally salvaged by any procedure because of digital gangrene advancing to the dorsum of the feet. Sympathectomy had been accomplished in these 2 cases in the hope that a major amputation might be avoided. If these 2 limbs are excluded from the series, then only 3 major amputations were required in limbs with absent pulsations below the femoral artery, an incidence of 12.0 per cent.

DISCUSSION

Peripheral obliterative arteriosclerosis is a progressive disease which ultimately may result in varying amounts of tissue necrosis if the patient survives long enough. Lumbar sympathectomy has been shown by many authors[1, 2, 3, 4, 5, 6, 8, 9] to be an effective procedure in improving the peripheral arterial circulation in many patients with obliterative disease. There is an increasing interest in the use of direct surgery on the obstructed femoral and iliac artery in an effort to provide major patent arterial channels to the lower legs. In this study of the early results of lumbar sympathectomy for obliterative arteriosclerosis, particular attention is placed on those extremities with absent arterial pulsations below the femoral or common iliac arteries, since limbs in this category may be potential candidates for direct arterial surgery. Of the total group of 49 sympathectomized limbs only 6 required a major amputation, an incidence of 12.2 per cent. If two virtually hopeless limbs are excluded from the group with arterial obstruction above the knee, the limb survival rate for this group is 88.0 per cent. Of the Type III and IV limbs with severe intermittent claudication 43.5 per cent were significantly improved, and 34.8 per cent were subjectively improved, or at least did not become worse. Only 21.7 per cent showed symptomatic progression or required amputation.

SUMMARY AND CONCLUSIONS

A follow-up study of results of lumbar sympathectomy for peripheral obliterative arteriosclerosis has been presented. Particular emphasis has been placed on the level of arterial obstruction. The authors believe that the rate of limb salvage and symptomatic improvement in these patients with markedly advanced disease is sufficiently encouraging to justify the continued use of lumbar sympathectomy in the treatment of peripheral obliterative arteriosclerosis.

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SOME PHYSIOLOGIC EFFECTS OF SHORT- AND LONG-TERM HYPOTHERMIA UPON THE LIVER

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EXPERIMENTAL evidence has been presented by Raffucci[13] and by Bernhard[1] that the hypothermic dog will survive total afferent hepatic vascular occlusion for one hour, whereas the mortality is 100 per cent in control normothermic animals. If this is true in humans as well, it should be feasible to perform partial removal of the liver in a dry field, and to increase the scope of resection when the tumor involves the portal vein by avoiding a high portal pressure. It has also been suggested by Bernhard that the use of hypothermia might be extended to include those patients with hepatocellular disease requiring anesthesia and surgery. Certainly it would seem proper that the effects of hypothermia itself upon the normal liver be first evaluated.

Such information is scanty. Utilizing the usual liver function determinants, such as Bromsulphalein retention, total protein, serum bilirubin, and flocculation tests, Bernhard[1] and Hallet[10] failed to demonstrate abnormalities following short periods of cooling. Likewise, a study of liver biopsies by the former revealed no change in liver architecture from that present before hypothermia.

In this laboratory during the last two years a systematic investigation of the effects of short and prolonged hypothermia has been undertaken. It has been reported by us[6] that practically all observations made in hypothermic animals showed changes which progressively increased with the length of hypothermia in spite of a stable temperature. As a phase of this study, the effects of hypothermia upon the liver were observed from 4 aspects, biliary secretion, in vitro oxygen consumption of the liver slice, composition of the liver, and hepatic blood flow estimation. Quantitative information concerning these 4 factors during short and prolonged cooling and following rewarming form the basis of this report.

METHOD

Mongrel dogs of both sexes fed the stock laboratory diet of "Friskies" were used for these studies.

Collection of Bile.—Bile was collected in 6 animals. In 5 of the 6 this was accomplished by inserting a stainless steel, double-flanged cannula into the duodenum opposite

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the opening of the common duct. This cannula was brought out through a stab wound in the right flank. After the gall bladder was removed and the cystic duct ligated, a short length of polyethylene tubing was inserted through the ampulla and anchored into the common duct by several ligatures snuggly tied around the duct and enclosed catheter. The end of the polyethylene tubing coming from the ampulla was permitted to lie free in the duodenum. Whenever bile collections were made the metal screw cap of the cannula was removed and the piece of tubing was withdrawn from the cannula so that bile could drain into a container. At the completion of the collection period the tubing was replaced in the duodenum allowing bile to flow freely into the intestinal tract. The metal cap was replaced to prevent loss of intestinal contents. These animals required no special care or diet and, at least during the experimental period, no biliary obstruction developed. In one animal the standard type of biliary fistula was created. Here, after removal of the gall bladder and ligation of the distal end of the common duct, a segment of polyethyelene tubing was anchored into the common duct. An attached rubber bag, in which bile was collected, was changed every 24 hours. In all animals, collections were made between 9 and 10 A.M. and 3 and 4 P.M. Animals were fed daily at the same time. These animals were preliminarily conditioned so that they stood quietly on the experimental table during sampling. After 6 to 14 days of collection of control samples, animals were subjected to 1 hour of open-drop ether anesthesia. Bile was collected during the administration of anesthetic and at the usual times, twice daily following this, until cholic acid production was at the control level. Since ether was the anesthetic agent used in the induction of hypothermia, these observations served as controls for the effect of this agent upon cholic acid production. All animals were subjected to 2 periods of hypothermia, one of 6 hours and the other of 12. Continuous hourly samples of bile were collected during the entire period of reduced body temperature. After rewarming, bile collection was made in the same manner as during the control period, that is, twice a day.

The technique of production of hypothermia used in all animals was as previously described in detail.[6] Essentially it consisted of placing the animal, lightly anesthetized with ether, into a thermostatically controlled water bath at 1° C. until the animal's temperature, as measured rectally, was 29° C. After removal from the bath, it was placed in an air-conditioned room, the temperature of which was adjusted depending upon the temperature of the dog. After a period of about 1 hour, required for stabilization, all temperatures were maintained between 22° and 24° C. for the duration of the experiment. At no time was it necessary to institute positive pressure respiration. Rewarming was effected by placing the animal in a warm-water bath (40° C.) until its body temperature was 30° C. It was then removed from the bath and allowed to continue to rewarm at room temperature. In all animals an interval of 10 to 14 days was permitted to elapse between the 6- and 12-hour periods of hypothermia.

In the one animal with the total biliary fistula the hourly collections of bile twice a day were carried out as well as the 24-hour measurements.

Determination of cholic acid was by the method of Irvin, Johnston, and Kopala.[12]

Oxygen Consumption and Tissue Analysis.—The O_2 uptake of liver slices was determined by the Warburg method according to Umbreit, Burris, and Stauffer[15] at 37° C. With a Stadie-Riggs Microtome uniform slices 0.5 mm. in thickness were obtained and placed in a beaker of Kreb's Ringer solution surrounded by crushed ice. The slices were then weighed and transferred to manometer flasks containing oxygenated Kreb's Ringer phosphate buffer (pH 7.4). One half of the flasks contained 0.5 ml. glucose substrate (0.018M) in the sidearm which was tipped in after the oxygenation period (10 minutes) and prior to equilibration. The total volume of fluid in all flasks was the same, that is, 3 ml. The center well of each flask contained 0.2 ml. of 20 per cent KOH and a fold of filter paper. Q_{O_2} values are expressed as μ liters of O_2 taken up per milligram of dry weight per 4 hours. The results were treated statistically with the use of Fisher's t-table.

The technique of handling samples, and methods of analysis for glycogen, total nitrogen, protein nitrogen, fatty acid, and percentage of water have all been previously described.[5] Results are expressed as grams per 100 grams of wet liver.

Hepatic Blood Flow and Splanchnic Oxygen Consumption.—Estimated hepatic blood flow (EHBF) was determined using the Bromsulphalein (BSP) method as described by Bradley[3] and used by us in previously reported studies.[7, 14] Prior to cooling, catheters were placed in a hepatic vein via the external jugular vein and into the femoral artery. In many of the animals, 7 to 10 days before the induction of hypothermia, a polyethylene cannula was inserted into the portal vein through the coronary vein and was brought out of the dog through a stab wound in the right flank. In some of these, catheters were also inserted into the external jugular vein, the inferior vena cava, just below the diaphragm, and the right heart. No priming dose of BSP was given to any of the animals and the amount of BSP injected was decreased with the length of hypothermia. Simultaneous samples of blood were withdrawn from the hepatic vein and femoral artery 20, 30, and 40 minutes after the onset of infusion, for determination of plasma BSP concentration. In instances with the 30-minute pair of samples, blood was concurrently withdrawn from the other catheters.

The oxygen content of hepatic vein and femoral artery blood was determined on samples withdrawn in sealed heparinized syringes containing sufficient mercury for mixing. These were maintained under refrigeration until analyses were made. The Goldstein[9] manometric technique for the determination of oxygen in blood in the presence of low concentrations of ethyl ether was used.

RESULTS

Bile Secretion.—Although the volume of bile and concentration of cholic acid varied from dog to dog, findings for all 6 animals were essentially the same. Results were typical of those found for dogs 98A and 158A (Figs. 1 and 2), the latter being the dog with the total biliary fistula. Controls showed no difference in cholic acid concentration (milligrams per cubic centimeter) between morning and afternoon samples. However, except for Dog 158A, where values were similar, the volume of bile obtained in the morning was greater than in the afternoon. Thus any change in total hourly cholic acid production could be ascribed to the difference in volume of bile secreted rather than to a decreased concentration.

Bile collected during the hour of ether anesthesia demonstrated a decreased volume but no change in milligrams per cubic centimeter concentration. This is typically shown by Dog 98A, in which the mean volume was 7.5 ± 1.8 ml. per hour in 26 control samples, and 2.6 ml. during the hour of ether. In the same controls, the concentration of cholic acid was 17.1 ± 4.7 mg. per cubic centimeter and during anesthesia it was 17.3 mg. per cubic centimeter.

Six hours after completion of the anesthetic, bile was collected for 1 hour in all animals. This was equivalent in time to the afternoon control collections. The volume in all animals was at the control level, whereas there was a sharp decrease in milligrams per cubic centimeter concentration of cholic acid. By the next morning (24 hours after ether) volumes and concentration were normal in all but 1 animal. After 48 hours the concentration was similar to that of the controls in this one.

All animals during the 6 and 12 hours of hypothermia continued to secrete bile. The volume, however, was markedly decreased, and, for the

most part, was 1 ml. or less per hour. The typical response to hypothermia is shown by Dog 158A. This animal, whose control bile volume was 5.7 ± 1.1 ml. per hour, secreted only 1.0 ml. of bile in the first hour of hypothermia. During this time the temperature decreased from 27° to 23° C. For the rest

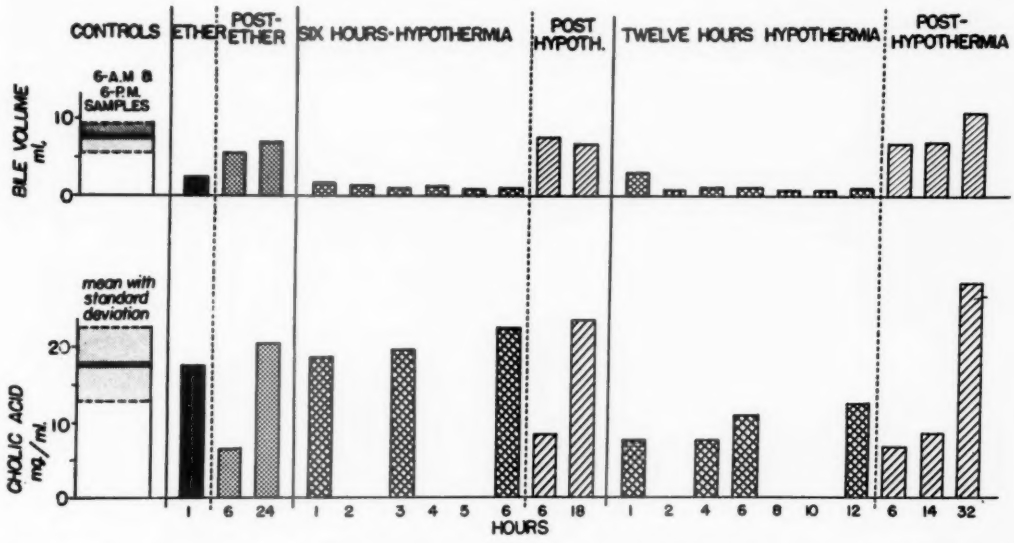

Fig. 1.—Effect of 1 hour of ether, and 6 and 12 hours of hypothermia upon bile volume and total cholic acid concentration (Dog. No. 98A).

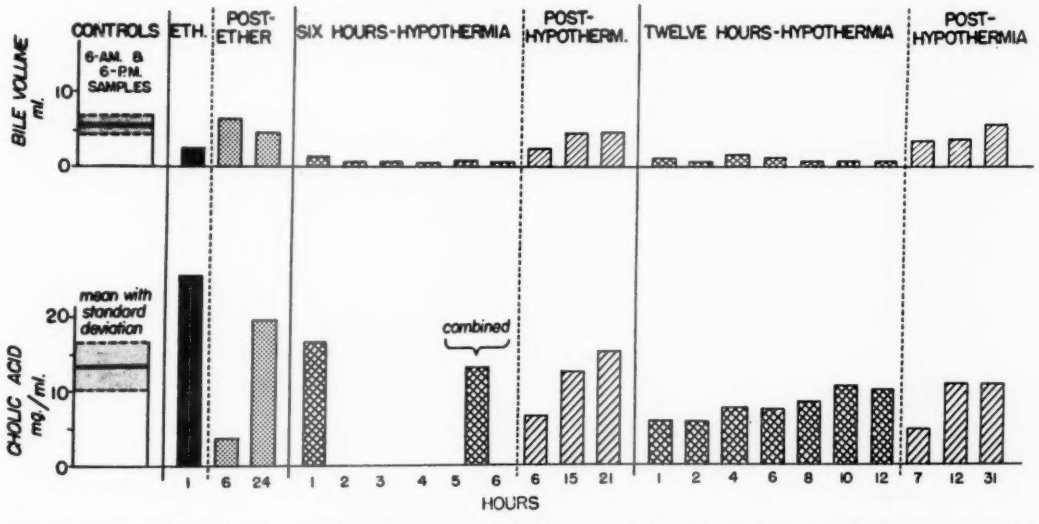

Fig. 2.—Effect of 1 hour of ether, and 6 and 12 hours of hypothermia upon bile volume and total cholic acid concentration (Dog No. 158A).

of the 6- and 12-hour periods of cooling, temperatures were maintained between 22° and 23.5° C. The bile volume gradually decreased so that it was only 0.4 ml. in the twelfth hour of hypothermia.

In spite of the marked reduction in biliary secretion, cholic acid concentration was not as severely affected by cooling. In Dog 158A during the 6-hour hypothermia experiment the concentration was within normal limits.

In the 12-hour experiment, after a slight initial drop, the concentration returned to the control level where it remained during this prolonged period of cooling. In none of the animals was there a significant depression of cholic acid concentration during the cooling period.

While the animals were being rewarmed, bile was collected and no increase in either volume or cholic acid concentration was found to occur as the temperature was raised. A 1-hour collection approximately 6 hours after body temperatures were normal revealed variable response in so far as volume was concerned. In Dog 98A there was a return to normal volume by this time, following both 6 and 12 hours of hypothermia. The volume of 158A did not reach the normal control level, however, until 15 hours after 6 hours of hypothermia and 31 hours after 12 hours of hypothermia. In the other 4 animals bile volumes were again normal between 6 and 24 hours after the shorter period of cooling, and 18 and 48 hours following the longer.

The time for return to normal concentration of cholic acid following the decrease that occurred following rewarming varied with the length of hypothermia. Following 6 hours of reduced body temperature the total cholic acid was back to the control level by 24 hours, and after 12 hours of cooling it took as long as 48 hours for this to take place.

TABLE I. OXYGEN UPTAKE AND GLYCOGEN CONTENT OF LIVER SLICE BEFORE AND AFTER HYPOTHERMIA

NUMBER OF DOGS	HOURS COOLED	QO_2		GLYCOGEN (PER CENT)
		WITHOUT GLUCOSE	WITH GLUCOSE	
12	0	10.6 ± 1.1	10.6 ± 1.3	3.5 ± 0.3
15	1-5	11.2 ± 1.8	11.6 ± 2.4	1.4 ± 1.3
8	6-11	5.4 ± 1.6	5.9 ± 1.7	1.5 ± 0.9
10	12-28	5.1 ± 1.3	5.9 ± 2.0	0.4 ± 0.2

Oxygen Consumption and Composition of Liver.—In Table I mean values for the O_2 consumption and glycogen content of liver of normothermic and hypothermic animals are presented. Fifteen animals, maintained from 1 to 5 hours at 22 to 24° C. showed no significant change in O_2 consumption even though there was a significant drop (P .01) in the liver glycogen. In animals cooled 6 to 10 hours, glycogen was maintained at a level similar to that during the 1- to 5-hour period. A significant decrease (P .001) in O_2 uptake occurred in this group. Dogs maintained hypothermic for from 12 to 28 hours demonstrated no further decrease in O_2 consumption from the 6- to 10-hour period, but there was a further depression (P .001) of the

TABLE II. COMPOSITION OF DOG LIVER BEFORE AND AFTER HYPOTHERMIA

NUMBER OF DOGS	HOURS COOLED	H_2O (PER CENT)	TOTAL (PER CENT) NITROGEN	PROTEIN NITROGEN (PER CENT)	NON-PROTEIN NITROGEN (PER CENT)	PROTEIN (PER CENT)	FATTY ACIDS (PER CENT)	GLYCOGEN (PER CENT)
12	0	72.6 ± 2.0	28.2 ± 2.1	23.4 ± 2.0	4.8 ± 0.3	14.8 ± 1.1	4.6 ± 1.0	3.5 ± 0 3
7	1-5	74.4 ± 1.4	26.6 ± 1.4	19.3 ± 1.1	7.3 ± 1.9	12.1 ± 0.6	3.2 ± 1.1	1.5 ± 1.2
10	6-11	73.8 ± 1.5	28.9 ± 2.3	21.1 ± 2.2	7.8 ± 1.8	13.2 ± 1.3	4.2± 0.8	1.3 ± 1.0
6	12-28	72.8 ± 1.2	29.6 ± 4.2	20.2 ± 2.3	9.5 ± 1.9	13.3 ± 0.7	4.8 ± 0.6	0.4 ± 0.3

glycogen level. These data seem to indicate that after the sixth hour of hypothermia some oxidative mechanism is interfered with, and that there is no direct relationship between the liver O_2 uptake and glycogen level.

The composition of the liver of normal and cooled animals is presented in Table II. In order to ascertain whether a relationship existed between liver composition and O_2 uptake, animals were grouped into periods of hypothermia similar to those in Table I. No statistical difference in water content and total nitrogen between the normothermic and any of the cooled groups was found. There was, however, a significant decrease in the glycogen, protein nitrogen, protein, and fatty-acid levels in animals cooled 1 to 5 hours. The protein nitrogen and protein remained at the lower level during the longer periods of hypothermia, but the fatty-acid content was restored to normal. Glycogen levels were similar to those in Table I. Animals during all hypothermic periods showed a significant increase (P .001) in the nonprotein nitrogen over the normal. There was a significant rise (P .01) in the 12- to 23-hour period over the 6- to 11-hour group, indicating a "piling up" of nonprotein nitrogen.

Information concerning O_2 consumption and composition of the liver in animals cooled either 6 or 12 hours and then rewarmed is presented in Table III. After a 6-hour period of hypothermia, dogs rewarmed demonstrated no significant difference, aside from glycogen content, from the normothermic animals. Liver samples were obtained 4 to 8 hours from the onset of rewarming. Rectal temperatures were back to the precooling level in all instances. These data indicate that even though there are statistically significant changes in liver composition during the first 6 hours, as shown in Table II, the changes are not irreversible and that the mechanism of O_2 uptake is not permanently depressed.

Animals maintained hypothermic for 12 hours and then rewarmed also demonstrated the reversibility of the changes in O_2 consumption and composition indicated in Tables I and II. Aside from the glycogen content, the composition of the liver in these animals was not significantly different from that of those with normal body temperature. In 3 of the 5 animals QO_2 values were significantly above normal. This finding would again tend to indicate that the glycogen content of the liver and the oxygen uptake of the liver slice have no direct relationship. It is to be noted that the average liver glycogen content in animals rewarmed after 6 hours of hypothermia is similar to that of the animals cooled 6 to 11 hours, and that the amount of glycogen in livers of animals rewarmed after 12 hours of hypothermia is similar to the content in the 12- to 28-hour hypothermic dogs. From these findings it would seem that liver glycogen depleted during hypothermia is not easily replaced regardless of the blood glucose level (Table III). In experiments (not listed) where blood glucose levels were maintained between 200 to 300 mg. per cent by constant infusion of glucose solution, liver glycogen was not restored.

Hepatic Blood Flow (EHBF) and Splanchnic Oxygen Consumption.— Forty-nine determinations of hepatic blood flow were performed on 35 animals maintained hypothermic for from 1 to 24 hours. To facilitate presentation

TABLE III. OXYGEN UPTAKE AND COMPOSITION OF DOG LIVER AFTER HYPOTHERMIA AND REWARMING

DOG NUMBER	HOURS COOLED	HOURS RE-WARMED	QO_2		GLYCOGEN (PER CENT)	TOTAL NITROGEN (PER CENT)	NON-PROTEIN NITROGEN (PER CENT)	PROTEIN NITROGEN (PER CENT)	PROTEIN (PER CENT)	FATTY ACIDS (PER CENT)	H_2O (PER CENT)	BLOOD GLUCOSE (MG. PER CENT)
			WITHOUT GLUCOSE	WITH GLUCOSE								
43A	6	5	11.9	10.1	2.0	29.6	7.6	22.0	13.8	5.3	74.4	116.1
92A	6	6	12.9	11.7	1.9	30.5	3.4	27.4	17.1	4.6	73.4	103.4
81A	6	6	12.0	11.7	0.4	29.6	4.0	25.6	16.0	4.6	74.0	107.2
69A	6	7	8.1	9.7	4.6	20.4	3.2	23.6	12.8	5.2	74.8	118.9
8A	6	7	9.3	7.7	0.5	27.2	5.6	21.6	13.5	4.9	73.7	108.6
			10.8 ± 1.8	10.2 ± 1.5	1.9 ± 1.5	27.5 ± 3.7	4.7 ± 1.6	24.0 ± 2.2	14.6 ± 1.6	4.9 ± 0.9	74.1 ± 1.7	110.8 ± 5.7
89A	12	4	10.9	11.2	0.4	31.7	4.3	27.4	16.8	4.7	75.5	192.0
204A	12	6	23.8	26.4	0.5	30.2	7.9	22.3	13.9	5.0	74.3	115.5
244A	12	8	19.0	18.7	1.2	30.9	5.0	25.9	16.2	5.2	71.0	----
693	12	6	10.3	9.7	0.1	28.8	4.2	24.6	15.4	6.1	72.9	52.8
253A	12	6	17.4	18.4	0.1	29.2	3.9	25.3	15.8	3.6	71.8	----
			16.3 ± 5.1	16.9 ± 6.0	0.5 ± 0.4	30.2 ± 1.1	5.1 ± 1.5	25.1 ± 1.7	15.6 ± 1.0	4.9 ± 0.8	73.1 ± 1.6	----

TABLE IV.

A. VALUES FOR HEPATIC BLOOD FLOW IN NORMOTHERMIC AND HYPOTHERMIC DOGS

NUMBER OF OBSERVATIONS	HOURS COOLED	TEMPERATURE (° C.)	EHBF*		E_{BSP}† (PER CENT)	P_{BSP}‡ (MG. PER CENT)	RATE (MG. PER MIN.)
			ML./MIN.	ML./KG./MIN.			
10	0	--------	803 ± 277	70.0 ± 4.1	29.0 ± 9.3	1.2 ± 0.7	1.14 ± 0. 2
10	1-2	23.0 ± 0.1	605 ± 227	39.6 ± 13.3	13.0 ± 3.4	2.9 ± 0.2	0.98 ± 0. 2
14	3-4	23.1 ± 0.6	616 ± 200	38.0 ± 10.3	16.0 ± 10.2	2.4 ± 0.3	0.88 ± 0.07
11	6	23.0 ± 0.2	365 ± 186	23.0 ± 9.0	21.0 ± 8.0	2.3 ± 0.2	0.66 ± 0. 2
8	8-13	23.1 ± 0.1	255 ± 110	19.0 ± 7.2	25.0 ± 12.8	2.6 ± 0.3	0.61 ± 0.01
6	18-24	23.0 ± 0.2	203 ± 37	13.0 ± 3.0	21.0 ± 10.0	2.9 ± 0.7	0.46 ± 0. 2

B. VALUES FOR HEPATIC BLOOD FLOW IN ANIMALS REWARMED FOLLOWING HYPOTHERMIA

NUMBER OF OBSERVATIONS	HOURS COOLED	HOURS REWARMED	TEMPERATURE (°C.)	EHBF*		E_{BSP}† (PER CENT)	P_{BSP}‡ (MG. PER CENT)	RATE (MG. PER MIN.)
				ML./MIN.	ML./KG./MIN.			
4	6	6	38.9 ± 0.9	1362 ± 344	82.0 ± 18.0	23.0 ± 7.0	1.0 ± 0.3	1.53 ± 0.5
5	12	6	37.3 ± 1.6	799 ± 241	67.0 ± 35.5	23.7 ± 6.1	1.7 ± 0.6	1.32 ± 0.2

*EHBF = Estimated hepatic blood flow.
†E_{BSP} = Per cent extraction of bromsulphalein.
‡P_{BSP} = Peripheral plasma concentration of bromsulphalein.

of the findings, they have been grouped according to the length of hypothermia and are presented in Table IV, A. The temperatures of all animals were maintained between 22.5° and 23.5° C. Since ether was used as the anesthetic during the induction of hypothermia, blood flow determinations performed on 10 animals anesthetized for 1 hour with this agent were used as controls. These data have been presented in detail.[7] Irrespective of the fact that temperatures were maintained constant, as the hours of hypothermia progressed, the values for the EHBF declined. Through 4 hours of hypothermia the mean blood flows were slightly over one half the control value of 70.0 ± 4.1 ml. per kilogram per minute. At 6 hours, the average EHBF of 23.0 ± 9.0 ml. per kilogram per minute was about one third the control level, and this continued to decrease so that, by 24 hours, values were 18 per cent of those for the normothermic animals. Extraction of BSP (E_{BSP}) was greater than 10 per cent in all instances, fulfilling the requirement proposed by Bradley. It was of interest to find that, although this value was not as great in the early hours of hypothermia, it approached the control level of 29 per cent in the longer term animals.

TABLE V. SPLANCHNIC OXYGEN CONSUMPTION IN HYPOTHERMIC ANIMALS

NUMBER OF OBSERVATIONS	HOURS OF HYPOTHERMIA	TEMPERATURE (° C.)	P_{O_2}* (VOL. PER CENT)	H_{O_2}† (VOL. PER CENT)	$P_{O_2} - H_{O_2}$ (VOL. PER CENT)	EHBF‡ (ML./MIN.)	SPLANCHNIC O_2 CONSUMPTION	
							(ML./MIN.)	(ML./KG./MIN.)
7	1-2	23.0 ± 1.4	24.9 ± 1.8	21.7 ± 2.8	3.2 ± 1.6	616 ± 247	16.8 ± 1.9	1. 1 ± 0.05
12	3-4	23.0 ± 0.6	24.9 ± 1.7	22.4 ± 1.5	2.5 ± 1.0	640 ± 152	14.9 ± 6.1	0. 9 ± 0.03
4	6	23.3 ± 0.2	22.0 ± 2.7	19.6 ± 3.0	2.4 ± 0.1	350 ± 210	8.5 ± 5.3	0. 5 ± 0.02
7	8-13	23.2 ± 0.1	20.4 ± 5.4	13.5 ± 5.8	7.1 ± 1.9	321 ± 138	20.0 ± 8.3	1.36 ± 0.45
7	18-24	22.8 ± 0.6	21.9 ± 4.8	14.9 ± 6.6	7.0 ± 2.8	321 ±77.5	14.9 ± 4.8	0. 9 ± 0.03

*P_{O_2} = O_2 content of peripheral artery blood.
†H_{O_2} = O_2 content of hepatic vein blood.
‡ EHBF = Estimated hepatic blood flow.

Determination of EHBF in animals maintained hypothermic for 6 and 12 hours and then rewarmed (Table IV, B), showed in all instances a prompt return to the control level, and in 2 (cooled 6 hours) a significant increase above this value.

Splanchnic oxygen consumption varied little in the animals with prolonged hypothermia from that in the animals subjected to hypothermia of shorter duration, in spite of the decreasing EHBF (Table V). The increased magnitude of the difference in oxygen content of the peripheral and hepatic blood in the more prolonged hypothermia accounted for this. The reason for the lower splanchnic oxygen consumption in the 6-hour group is not apparent.

The question of the validity of the BSP method for determination of EHBF in hypothermia, was considered. Since one of the basic assumptions of the method is that the plasma concentration of BSP in the portal vein is equivalent to that in the peripheral arterial blood, it was felt necessary to establish this relationship in cooled animals. Therefore, samples of blood were withdrawn from the indwelling portal vein catheter for determination of BSP concentration, so as to coincide with the removal of the second pair of samples taken for measurement of the EHBF. Results are shown in Table VI. Through the first 6 hours of hypothermia there was no statistically significant difference in concentration between the simultaneously drawn samples, the change being less than 1 per cent. In the more prolonged periods of hypothermia the findings were less consistent. For example, although the mean per cent change following 14 hours of hypothermia was –9.6, the range in this group was from –1.3 to –13.1 per cent. It would thus seem that before a determination of blood flow in an animal hypothermic over 6 hours could be considered valid, this relationship must be known.

TABLE VI. PLASMA CONCENTRATION OF BSP IN SIMULTANEOUSLY DRAWN PERIPHERAL ARTERIAL AND PORTAL VEIN BLOOD SAMPLES DURING PROLONGED HYPOTHERMIA

NUMBER OF OBSERVATIONS	HOURS OF HYPOTHERMIA	CONCENTRATION OF BSP (MG. PER CENT)		PER CENT CHANGE
		PERIPHERAL ARTERY	PORTAL VEIN	
3	1	2.28 ± 0.2	2.28 ± 0.2	0.0
13	2	4.01 ± 1.17	3.97 ± 1.1	–0.9
3	3	2.06 ± 0.3	2.08 ± 0.3	+0.9
4	4	2.32 ± 0.4	2.30 ± 0.4	–0.9
13	6	2.11 ± 0.6	2.10 ± 0.6	–0.5
2	8	3.73 ± 0.2	3.66 ± 0.3	–1.8
5	12	1.75 ± 1.1	1.63 ± 1.1	–6.8
3	13	2.62 ± 0.2	2.65 ± 0.3	+1.1
4	14	3.76 ± 0.4	3.40 ± 0.4	–9.6

Similarly, when simultaneous samples were withdrawn from the jugular vein or right heart catheters and femoral artery, a variable relationship in BSP concentration was found to exist.

COMMENTS

In a previous report from this laboratory on some of the alterations resulting from cooling, it was concluded that prolonged hypothermia was not similar to hibernation or a state of relative physiologic inactivity, for, although

the temperature might remain stable at low levels, practically all observations made showed changes which became progressively more pronounced as the hours of hypothermia were extended. From this it was conjectured that perhaps the more complex and pronounced the changes become the more difficult would be their reversion to normal. That this is partly so, in so far as the liver is concerned, may be gathered from the greater length of time required for cholic acid to return to control levels following 12 hours of hypothermia than following 6 hours. It is significant, however, that 6 hours of hypothermia resulted in no greater change in the pattern of biliary secretion than did 1 hour of open-drop ether anesthesia in the normothermic animal. In view of the recent report by Popper[12] that it is still possible for the liver to produce bile with its blood supply markedly reduced, it is unlikely that the depression of volume of bile or posthypothermic decrease in cholic acid concentration can be ascribed to the reduction in blood flow during the hypothermia.

Similar to the findings of Burdette[4] in the dog and Fuhrman and Crismon[8] in the rat following 1 hour of hypothermia, no decrease in oxygen uptake of the liver slice was found in animals cooled (22.5° to 23.5° C.) for as long as 5 hours. In more prolonged hypothermia a significant decrease did occur. No relationship existed between the consumption of oxygen and composition of the liver. This is contrary to the report of Fuhrman and Crismon that such a relationship does exist between glycogen and oxygen uptake in the rat. The finding of an elevated liver Q_{O_2} in 3 of 5 animals, rewarmed following 12 hours of hypothermia, suggests that perhaps some enzyme system is interfered with and that an oxygen debt can occur. However, the values for the uptake of oxygen up to six hours of hypothermia agree with the findings of Bigelow and Lindsay[2] that temperatures remaining at low levels for as long as 4.3 hours did not produce an oxygen deficit in the tissues.

In the only other study reporting measurement of hepatic blood flow during hypothermia, Hallett,[10] using pentobarbital anesthesia in acutely cooled animals, found an arithmetic decrease in flow as the body temperature dropped. It was about 22 per cent of the normothermic level at 23° C. Findings reported in this study using ether anesthesia during induction of hypothermia demonstrate no similar pattern, the decrease in EHBF being more closely related to time of hypothermia than to temperature. Animals cooled as long as four hours demonstrated blood flows about 50 per cent of those for the normothermic ether-anesthetized animals but approximately 80 per cent of the level of the blood flow in normothermic animals anesthetized with Nembutal. In this laboratory, a group of the latter animals were found to have a hepatic blood flow of 49 ± 7.4 ml. per kilogram per minute[7] The validity of these relatively great flows in the early hours of hypothermia is substantiated by relating them to the findings for cardiac output in etherized hypothermic animals which will be subsequently reported. Here, likewise, the decrease in cardiac output in animals made hypothermic under ether anesthesia is not as pronounced as when Nembutal is used. The frequent finding of extrahepatic removal of BSP as the hours of hypothermia progress allows the validity of the BSP method for measurement of EHBF to be subject to

criticism. Since this extrahepatic loss of BSP would give a falsely high value for the rate of removal of BSP by the liver, the actual blood flow is probably lower than that calculated. Of course, this would also tend to invalidate the accuracy of the measurement of splanchnic oxygen consumption and of BSP extraction.

Of greater importance than the question of the quantitative validity of the BSP during hypothermia is the fact that rewarming following prolonged cooling resulted in a prompt return of normal blood flow in all animals studied.

SUMMARY AND CONCLUSIONS

The effects of short and prolonged (12 hours) hypothermia followed by rewarming upon biliary secretion, oxygen uptake of the liver slice, composition of the liver, and hepatic blood flow have been evaluated. Results of these observations revealed that:

1. Although bile volume is markedly decreased during hypothermia, milligram per cubic centimeter concentration of cholic acid is not similarly depressed. Following rewarming, the length of time required for the return to normal levels of volume and amount of cholic acid is dependent upon the length of hypothermia. After 6 hours of hypothermia the pattern of biliary secretion is similar to that following 1 hour of open-drop ether anesthesia.

2. A significant increase in the nonprotein nitrogen fraction of the liver composition occurs during hypothermia and a marked decrease in glycogen content is seen. The latter fails to return to normal following rewarming in spite of the level of blood sugar and/or the concentration of blood glucose.

3. No decrease in oxygen consumption of the liver slice was seen in up to 6 hours of hypothermia. Longer periods of cooling produced a significant decrease in Q_{O_2}. However, following rewarming, even after 12 hours of hypothermia, there was a return to normal or above-normal levels of consumption suggesting the possibility that a tissue oxygen debt can occur in animals cooled for a long time.

4. The validity of the measurement of EHBF with the use of the Bromsulphalein method of Bradley, after 6 hours of hypothermia, is open to criticism because of the extrahepatic loss of BSP. The decrease in blood flow through the liver is not as pronounced when ether is used as the anesthetic during induction of hypothermia rather than pentobarbital. Under conditions of these experiments, the hepatic blood flow seems to be more closely associated with duration of hypothermia rather than with the temperature level. Following rewarming after hypothermia up to 12 hours (22.5° to 23.5° C.) there is a prompt return to normal blood flow.

It may be concluded that hypothermia maintained at 22.5° to 23.5° C. for as long as 12 hours produces no irreversible changes in the liver in so far as biliary secretion, oxygen consumption, composition (excepting glycogen), and hepatic blood flow are concerned.

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THE REGENERATION OF THE LIVER IN THE MONKEY AND IN THE MONKEY WITH PORTACAVAL SHUNT

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IT HAS been known for many years that the liver will regenerate after chemical or surgical trauma. Ponfick, using dogs, first reported on this problem in 1894.[1, 4, 10, 14] Since then, rats, rabbits, and fowl have also been studied and have demonstrated essentially the same regenerative ability.

The effect of portacaval shunt has been studied in certain experimental animals. Because this operative procedure is widely used in the treatment of portal hypertension and bleeding esophageal varices, its effect on the regenerative power of the liver is of real clinical importance. Its effect is of increased importance since the patient who requires portacaval shunt has a diseased liver and needs its maximum regenerative power. Investigation in the portal system of dogs and most animals has been handicapped in its clinical application by the critical differences in the anatomy of these animals and man. This problem may be largely overcome by using the monkey who resembles the human being more closely anatomically than other experimental animals. Basic work in the portal system of the monkey was carried out in this institution by Child and his associates[1] several years ago. They showed the feasibility of acute portal vein ligation in the rhesus monkey and demonstrated that the portal system of the monkey closely resembles that of the human anatomically. Monkeys had not been used to study hepatic regeneration in the past because it is difficult to manage them in the postoperative period. Also, it was felt that hepatectomy was very difficult if not impossible to accomplish with survival in these animals. These problems have been overcome through assiduous teamwork on the part of the investigators and the animal men who are essential for the success of the project. The following is a report on partial hepatectomy in normal monkeys and in monkeys who have first been subjected to portacaval shunt.

METHODS

Macacus rhesus monkeys, whose weight averaged between 3 and 5 kilograms, were used. Animals smaller than this did not survive the operative procedure. Larger monkeys were too difficult to handle in the postoperative period and were frequently injured when attempts were made to catch them. King rhesus monkeys were obtained and served as blood donors for the procedures. Cross matching was not used before transfusions. The operative procedure has been described in detail in another communication,[3] so that only a brief description of the regional anatomy of the *Macacus rhesus* and

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operative procedure will be given. The liver consists of 4 main lobes and 2 smaller lobes. The larger are the left lateral, left medial, right medial, and right lateral. The caudate and quadate are much smaller and do not play a part in the operative technique. When the operative procedure is begun, the left lateral lobe is attacked first. This lobe is dissected free from the adjacent structures until it is attached by a small pedicle that can be secured, ligated, and divided. It is important to secure the hepatic vein which is located posteriorly so that it will not bleed or permit an air embolus. The right lateral lobe is subtotally resected using interlocking sutures of chromic catgut. Occasionally, the catgut sutures are reinforced with one or two sutures of fine silk. Periodically, traction on the liver is relaxed so that the inferior vena cava is not continually obstructed. Preparations are made to remove the last lobe which is the right medial or the gall-bladder lobe. First the cystic duct and artery are isolated, divided, and ligated with silk sutures. The common duct must be avoided by not going too low on the common pedicle of the cystic duct and artery. A strip of ribbon catgut 1 inch wide is used to hold the stitches in the liver parenchyma so that it is first placed and fixed with three sutures. Next, interlocking sutures are placed and each tied after the next one has been placed so as to avoid confusion that might arise with multiple sutures in the wound. The lobe is subtotally resected distal to the ribbon gut. Any small bleeding points are transfixed with fine silk. During the entire procedure the interlocking sutures must be placed at right angles to the liver substance and they must not be tied too tightly, so that they do not pull out or cut through. During the procedure the monkey receives 50 to 75 c.c. of blood and 100 to 125 c.c. of 5 per cent glucose in water with added vitamins C and K. Large doses of penicillin and dihydrostreptomycin are administered postoperatively for three days. The monkeys are allowed nothing by mouth for two to four days depending on their general condition and activity. During this period they receive infusions. Preferably they have a visible bowel movement before they are fed but occasionally they are fed prior to this event. Their blood sugar must be maintained at satisfactory levels postoperatively. Because several animals have died from overloading of the vascular system with fluid, 50 per cent glucose with its high sugar content and low fluid volume has been used with good results.

In another group of monkeys, portacaval shunts were performed by an end-to-side method using interrupted everting mattress sutures of No. 5-0 arterial silk. These animals usually required no blood and were able to eat at an earlier date than the hepatectomized monkeys. Postoperative care was less difficult. Hepatectomy was performed about two weeks later. The animals that survived both operations were kept for two months and then sacrificed by exsanguination. At the time of sacrifice, the liver specimens were weighed and compared to the theoretical remnant. The hepatic regeneration was then calculated.

The determination of the average extent of hepatectomy performed was accomplished in the following manner: Sixteen of the animals who died immediately or in the first 24 hours after surgery were examined and the

per cent of liver removed calculated from the amount found in situ at autopsy. The amount resected was added to the amount remaining and thus the total weight was found. It was then possible to determine the per cent of hepatectomy for that animal by dividing the amount resected by the total liver weight. Using this method for the 16 animals, it was found that the average liver resection was 53.4 per cent. The standard error was 7.1 per cent. This correlated much better with the results than when the average hepatectomy was calculated on the basis of body weight. See Table I for details.

TABLE I. CALCULATION OF PER CENT HEPATECTOMY

	AMOUNT REMOVED (GRAMS)	REMNANT (GRAMS)	TOTAL WEIGHT OF LIVER (GRAMS)	PER CENT HEPATECTOMY
1	32.0	21.0	53.0	60.4
2	34.3	58.0	62.3	55.4
3	102.0	112.3	214.3	47.7
4	71.0	54.0	125.0	56.7
5	68.15	49.0	117.15	58.3
6	45.3	34.0	79.3	57.8
7	67.1	58.6	125.7	53.6
8	57.0	61.6	117.6	48.7
9	65.9	77.3	143.2	46.2
10	51.5	38.4	89.9	57.3
11	45.0	42.0	87.0	51.8
12	65.0	61.0	126.0	51.6
13	65.0	67.0	132.0	49.3
14	61.0	63.0	124.0	49.2
15	78.8	59.0	137.8	57.2
16	67.6	58.0	125.6	53.8
53.4 per cent average taken				

It had been attempted to determine the extent of hepatectomy based on the per cent of liver in relation to body weight. In studying 42 animals, it was found that the per cent of liver to body weight varied from 2 to 5 per cent so that by using this technique it would be impossible to predict accurately the extent of hepatectomy.

RESULTS

Eight of 28 monkeys survived hepatectomy alone. In developing a standard technique, other procedures were used on 16 monkeys and there were several survivors, but they will not be used in the study of regeneration. The high mortality was in the early phases of the experiment. Two deaths were due to liver failure, and 2 were due to intestinal obstruction. Technical errors were responsible for the fatal outcome in 16 monkeys. The complete results in the study of regeneration are in Table II. All the monkeys lost weight in the postoperative period, and the average loss was 405 grams. These losses occurred even though the monkeys were eating well, were very active, and appeared to be in good health. The average regeneration in these monkeys was 26.8 per cent with a variation from minus 28 per cent to plus 76 per cent. A standard error was not determined as the variation is too wide.

Microscopic sections were obtained in all the animals that survived. They were obtained at the time of hepatectomy and at the time of sacrifice two months later. Preoperatively all the animals had histologically normal

livers. At the time of sacrifice, the livers appeared to be grossly hypertrophied and the edges were rounded and firm. There was no evidence of regeneration at the edge of the resected tissue. The microscopic sections at this time revealed normal liver parenchyma.

TABLE II. LIVER REGENERATION IN NORMAL MONKEY

ANIMAL NO.	PREHEPATECTOMY BODY WEIGHT (GRAMS)	BODY WEIGHT AT TIME OF SACRIFICE (GRAMS)	WEIGHT OF LIVER REMOVED (GRAMS)	THEORETICAL REMNANT (GRAMS)	ACTUAL REMNANT (GRAMS)	PER CENT CHANGE IN WEIGHT OF LIVER
39	3,130	2,930	61.2	52.2	52.8	+ 0.1
37	3,118	?	63.9	54.1	64.2	+18.7
72	3,600	3,400	66.1	56.3	40.3	-28.4
76	3,877	3,527	52.6	46.6	82.0	+75.9
83	3,855	3,250	58.2	42.7	65.0	+52.2
84	3,644	3,300	53.8	46.2	77.2	+67.1
85	3,650	3,360	63.5	54.1	67.6	+24.9
103	4,890	4,050	84.2	71.5	87.9	+22.9
Average	3,402	3,807	61.9	52.9	67.1	+26.8

Four simians were subjected to both hepatectomy and shunt in one stage. The procedure lasted about three and one-half hours. All the animals died in the early postoperative period. At present it is felt that the one-stage operation is too massive for animals to survive.

Portacaval shunt was carried out in 29 animals with 10 deaths. In addition, 3 animals were doing poorly clinically and were deliberately sacrificed at variable times in the postoperative state. A clotted anastomosis was found in 1 and in the other 2 no definite cause was found for the poor course. As was outlined in the method, the plan was to wait two weeks and then carry out the hepatectomy. In earlier stages of the study, some of the monkeys waited several months before they had the second stage. The simians invariably lost weight, in several instances up to 25 per cent of their original weight. Hepatectomy was carried out on 16 monkeys with 6 long-term survivors. There were also 4 monkeys which survived the operation and died up to nine days postoperatively. These latter animals all did well immediately after surgery but then became more or less lethargic. In one case, jaundice developed terminally. The diagnosis of liver failure was based on their dramatic response to intravenous glucose. The response was more striking in the earlier stages than in the terminal phases. Some of these monkeys had convulsive seizures that were stopped by the glucose. In the animals that died of liver failure, marked fatty infiltration of the liver was demonstrated at post-mortem examination.

The animals that were followed after both portacaval shunt and hepatectomy lost 5.7 per cent of their theoretical hepatic remnant during the postoperative period. This indicates that no significant regeneration took place. They lost an average of 500 grams of body weight following the second operation. Grossly the remaining liver had a sharp edge with no evidence of growth. Usually the livers were soft and yellowish in appearance. Sections revealed varying degrees of fatty infiltration. The degree of fatty change was always less than that seen in the 4 animals that died of liver failure.

The exact statistical analysis is presented in Table III.

TABLE III. LIVER REGENERATION IN MONKEYS WITH PORTACAVAL SHUNT

ANIMAL NO.	PRE-SHUNT BODY WEIGHT (GRAMS)	PRE-HEPATECTOMY BODY WEIGHT (GRAMS)	BODY WEIGHT AT SACRIFICE (GRAMS)	WEIGHT LIVER REMOVED (GRAMS)	THEORETICAL HEPATIC REMNANT (GRAMS)	ACTUAL HEPATIC REMNANT (GRAMS)	PER CENT CHANGE
54	3,110	2,610	2,450	44.9	38.3	37.2	-2.4
86	4,317	4,050	3,840	49.2	43.6	57.0	+27.2
99	3,960	3,710	3,260	64.8	56.8	59.7	+5.1
102	4,210	4,300	3,310	54.0	47.0	58.0	+21.0
105	3,910	3,590	3,045	59.2	51.7	45.5	-12.0
106	3,910	3.940	3,290	91.3	79.5	40.0	-50.0
Average	3 903	3,700	3,199	63.9	52.6	49.6	-5.7

DISCUSSION

The evaluation of these results will be considered in two sections. First the results in the normal will be considered and then the monkeys with portacaval shunt will be discussed.

The average regeneration in those with hepatectomy alone is apparently lower than that reported in other experimental animals. It is felt that this is merely an expression of the monkey's higher level on the phylogenetic scale. Higgins and Anderson[7] reported that rats would regenerate over 200 per cent of the resected segment. Dogs will regenerate up to the 100 per cent mark but it is less than rats.[2, 4, 10] No definite figures are available for the rabbit or the fowl except as in relation to the variations of the blood supply and its effect.[8, 17] While there are wide variations in the group here reported and it is not large enough for definite conclusions, it is obvious that significant regeneration occurs in the liver of these animals. Another point to speculate on is whether the hepatectomy performed may not call forth a maximal stimulus to regeneration.

The results in the portacaval shunt group parallel those that have been reported in other animals with this variation in blood supply. Occlusion of the portal vein or shunting of the blood from the liver to another vein has always markedly decreased the regenerative power of the liver in other animals. It is difficult to keep dogs alive for an adequate period of study when the 70 per cent hepatectomy is carried out in conjunction with a portacaval shunt. Child and his associates[2] from this laboratory were unable to keep a dog alive for more than 29 days after hepatectomy and shunt. In 1922, Mann and Magrath[13] reported that the only way to produce a true liver insufficiency in the dog was to perform an Eck fistula and a hepatectomy. In rabbits, which have a bilobed portal system, Rous and Larimore[17] occluded the portal vein and noted atrophy in the liver supplied by this vessel. The remaining liver hypertrophied and there was no sign of liver insufficiency. In rats with partial portal ligation, the regeneration was decreased to 76 per cent in Stephenson's[19] series. Thus an adequate blood supply is essential for liver regeneration. Mann felt that there was something in the portal blood that stimulated regeneration. This feeling has not been completely substantiated in dogs which will regenerate substantial amounts of liver following portacaval transpositions and hepatectomy. The effect of portacaval transposition on regeneration in the liver of the monkey will be the subject of a later report.

The most important clinical consideration of this study is whether portacaval shunt will harm a normal liver. The study indicates that it will. The animals with portacaval shunts did not tolerate the hepatectomy as well as the control simians and they showed marked fatty change in their livers. In applying these facts to human patients, it must be remembered that the cirrhotic patient with portal hypertension has already developed collateral circulation, so that most of the usual portal blood does not get to the liver.[9] This factor makes the shunt less of a loss to the cirrhotic patient than it would be to the normal person who has no significant collateral circulation.

SUMMARY AND CONCLUSIONS

1. Eight of 28 monkeys which were subjected to a standard hepatectomy survived the operation and were sacrificed at the end of two months.

2. The average hepatic regeneration in these animals was 26.8 per cent.

3. In 6 monkeys which survived both portacaval shunt and hepatectomy, there was no significant liver regeneration.

4. It is probable that removing the venous blood supply markedly restricts the regenerative power of the monkey liver.

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ACUTE GASTRIC ULCER

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ULCERATION of the stomach or duodenum may be either acute, subacute, or chronic. Acute ulcers, in contradistinction to chronic ulcers, present as small, multiple, superficial and clinically asymptomatic lesions, which tend to heal quickly.

Acute ulcers are seldom diagnosed because they are so silent in their symptomatology, yet according to gastroscopic examinations and post-mortem examination they are more common than usually reported.

These acute primary ulcers are usually multiple, but may also present as single lesions. They may appear anywhere in the stomach or duodenum in contrast to the chronic ulcer which is usually seen on the magenstrasse and in the first inch of the duodenum.

The acute ulcer is usually superficial and confined, at least in the beginning, to the mucous membrane. Should any factor exist which retards its rapid healing, it may penetrate into the muscularis mucosae and even deeper with occasional perforation through the muscle layer and serosa. It is during this process of penetration that blood vessels may be eroded and give rise to hemorrhage.

We wish to record three cases where massive upper gastrointestinal hemorrhages have been caused by such acute primary ulcers.

CASE REPORTS

CASE 1.—J. A. M., No. 7251, was a white man, aged 70 years. He was admitted to the Pretoria General Hospital complaining of a generalized feeling of weakness, of having passed a black stool the previous day, and of vomiting "coffee-ground" material.

Previous history: The patient felt absolutely normal until about a month previous to admission. Since then his appetite had diminished. He had no pain before or after meals, and there was no vomiting. He had noticed nothing particular in regard to his stools. The day before admission, while taking his daily stroll, he felt weak and had to sit down for a rest. The same evening he vomited some bright red blood.

Physical examination: The patient looked anemic. There was no jaundice. He was of spare build but there had been no recent loss of weight. Temperature 98° F., pulse 100 per minute and quite regular, blood pressure was 110/65. There were no dilated veins in the neck or around the umbilicus. The liver was enlarged about one finger, and the spleen was not palpable. There was slight tenderness in the epigastrium as well as over the liver area. Rectal examination was negative.

Physical examination of all the other systems was negative.

Provisional diagnosis: Bleeding from a gastric ulcer or possible esophageal varices.

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The patient was given 1,000 c.c. of blood and his general condition appeared satisfactory. During the next twelve hours there was no hematemesis and a Levin tube which was passed into the stomach returned no blood with washings. About fifteen hours after admission, the patient started to vomit again and on one occasion vomited about a pint of bright red blood. His general condition again deteriorated and more blood was administered. It was decided that he was probably bleeding from a gastric ulcer and a laparotomy with possible gastrectomy was indicated. After a further 1,500 c.c. of blood, his blood pressure rose to 110/60.

Operation: A right paramedian incision was made and a quick examination of the abdominal organs revealed nothing abnormal. The liver appeared normal, the spleen was not enlarged, and there was no sign of a hiatus hernia.

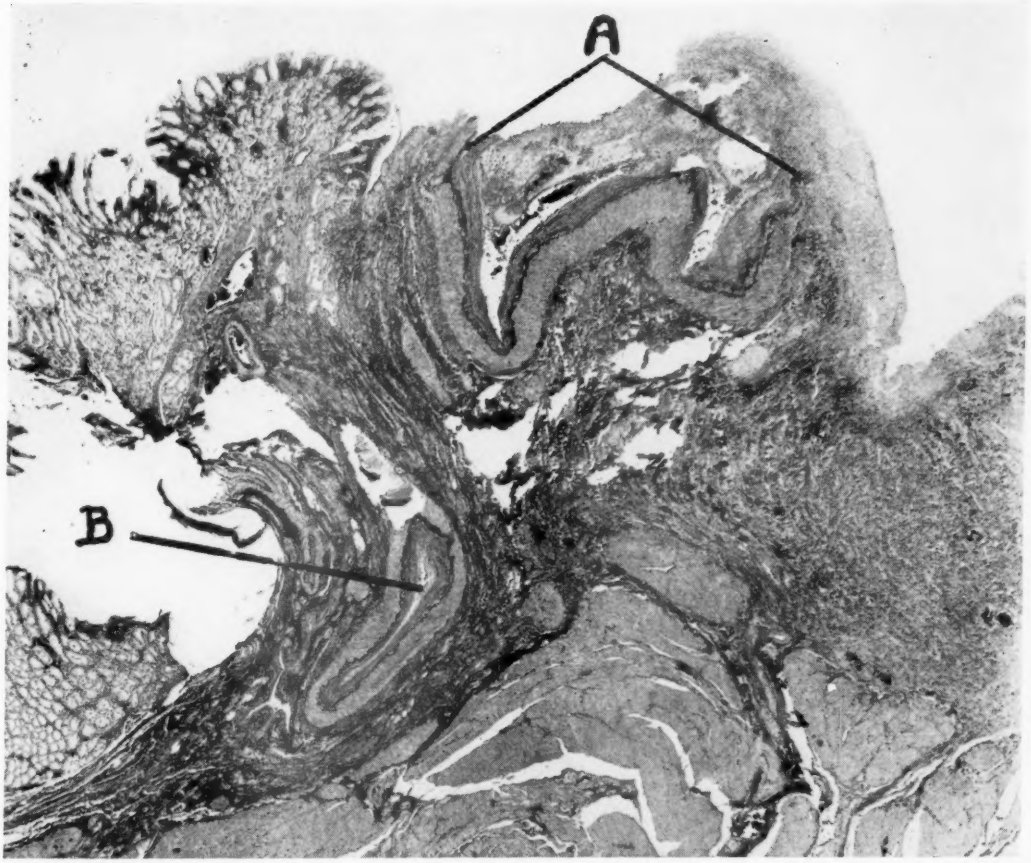

Fig. 1.—Part of stomach wall showing acute ulcer. Muscular layer intact. (*A*) Artery in mucosa with large rupture; (*B*) artery showing endarteritis (×20).

The stomach and duodenum were carefully inspected as well as palpated but nothing abnormal could be seen or felt. The lesser sac was opened, the posterior wall of the stomach inspected and the stomach itself palpated between the two hands, but there were no obvious lesions. After the peritoneal cavity was packed off, a large gastrotomy incision was made through the anterior wall, and the stomach cleared of massive blood clot. On the posterior wall of the stomach in the upper third was an ulcer, 1 cm. in diameter, and there was active bleeding from a vessel in the base of the ulcer. A figure-of-eight stitch was placed to control the bleeding and a partial gastrectomy was proceeded with, removing the ulcer with the specimen.

The patient made an excellent recovery and was discharged on the twelfth postoperative day.

Pathologist's report: The specimen consisted of a small portion of stomach wall containing an ulcer, 1 cm. in diameter. The ulcer was superficial and penetrated the mucosa, but not the muscular layer. The floor was covered by necrotic material and fibrin.

Sections showed a superficial gastric ulcer, the base of which consisted of granulation tissue extensively infiltrated by chronic inflammatory cells and covered by necrotic material and fibrin. In the center of the ulcer there was a large artery, approximately 1.1 mm. in diameter, the outer wall of which had been completely eroded (Fig. 1). The opening in the artery was partially filled with a fibrin plug. The ulcer had destroyed the mucosa and muscularis mucosae, although this was visible on both sides of the ulcer. The muscle layer was intact. Arteries in the submucous layer showed a moderate degree of endarteritis without thrombosis. The lymphoid tissue was not unduly prominent.

The mucosa, a few millimeters away from the ulcer, was 4.0 mm. in thickness. In the glands, the mucus-secreting cells extended down the tubules to an extent greater than that normally found, and, in a few instances, extended down to the bottoms of the tubules. The distribution of parietal and chief cells was normal. The interstitial tissue between the gastric glands showed a moderately marked infiltration by plasma cells, lymphocytes, and eosinophils with small collections of neutrophil polymorphs.

Histologic diagnosis: Subacute gastric ulcer with erosion of an artery. A moderate degree of chronic gastritis was also present.

CASE 2.—S. B., No. 7333, was a white woman, aged 69 years. She was admitted into the Pretoria General Hospital with severe hematemesis.

Previous history: She had had a cholecystectomy many years ago. During the last five years she suffered from no ailments. No history of pain or discomfort in the abdomen and no history of tarry stools. No loss of weight or disturbance of her appetite. She went to bed feeling quite well the previous evening, but felt sick during the night and started to vomit quantities of bright red blood.

Physical examination: This revealed an elderly woman in a shocked and anemic condition. Her pulse was 120 per minute but quite regular and her blood pressure was 115/70. She did not appear to have lost any weight.

On examination again there was nothing of note. The abdomen appeared slightly distended. The liver and spleen were not palpable. A rectal examination was negative.

A Levin tube was passed into the stomach, and a blood transfusion was started. Her general condition improved but three hours after admission she started to vomit large quantities of pure fresh blood again, despite saline solution irrigations via the Levin tube. The blood was given faster and it was decided to do a laparotomy and possible gastrectomy due to the possibility of bleeding gastric ulcer.

Operation: A right paramedian incision was made. A quick examination of the abdominal organs revealed nothing abnormal. The spleen was normal in size. There was no hiatus hernia. The gall bladder had been removed and the liver appeared normal. The stomach and duodenum were carefully inspected and palpated but nothing abnormal could be seen or felt. The lesser sac was opened and the stomach palpated between both hands but there was nothing pathologic to be seen or felt.

A wide anterior-wall gastrotomy was done after the peritoneal cavity was packed off, and the stomach cleared of clot and blood. High up on the lesser curvature about 4 cm. from the esophagus was an ulcer, about 2 cm. in diameter, with a spurting vessel in its base. The bleeding was controlled with a stitch and a partial gastrectomy of the Schoemaker type was done, removing the ulcer with the lesser curvature.

The patient recovered and was discharged from hospital on the thirteenth postoperative day.

Pathologist's report: The specimen consisted of a large part of the stomach and an ulcer, 2 cm. in diameter, received separately. This had apparently been removed from the lesser curvature about 4 cm. below the cardiac opening. The ulcer was of superficial nature and the floor was covered with coagulated blood and fibrin.

Sections showed a superficial gastric ulcer extending through the mucosa and muscularis mucosae to the submucosa (Fig. 2). The muscle layer remained intact. The general microscopic features were essentially similar to the previous case with the important difference that reactive endarteritis was minimal.

In the floor of the ulcer an artery, 1.2 mm. in diameter, was present. The outer part of the wall of the artery had undergone necrosis and merged into the necrotic floor of the ulcer. In serial sections this artery was seen to have ruptured and to be partially filled with a fibrin plug.

A few millimeters away from the ulcer the mucosa was 1.2 mm. thick and was diffusely infiltrated by plasma cells, with a few eosinophils and lymphocytes and occasional neutrophil polymorphs. This interstitial infiltration was distinctly more marked in the superficial area of the mucosa, while in the deeper part, the lymphoid follicles were prominent. The distribution of chief and parietal cells in the gastric glands was normal.

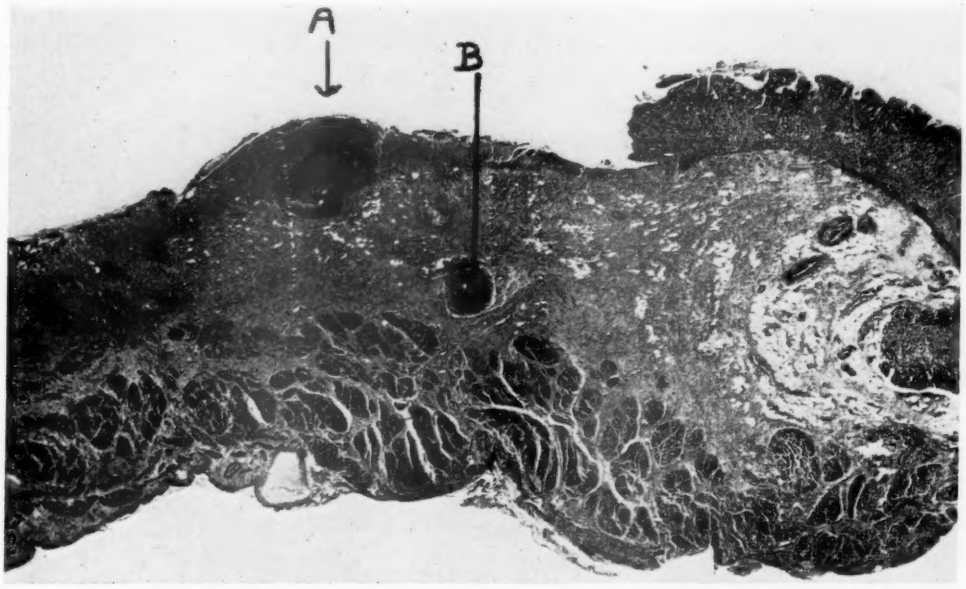

Fig. 2.—Whole thickness of stomach wall. Large superficial ulcer. Intact muscle layer. Mucosa present at upper right. (*A*) Superficial artery with necrotic wall; (*B*) artery filled with thrombus. (×11; reduced ⅙.)

Histologic diagnosis: Acute peptic ulcer with erosion of an artery. A moderate degree of chronic gastritis was present.

CASE 3.—W. S., No. 7228, was a white woman, aged 75 years. She was admitted into the Pretoria General Hospital with severe hematemesis.

Previous history: This patient was absolutely normal previous to admission. She had had a normal dinner the evening before and went to bed as usual. Just after midnight she woke feeling nauseous and vomited about a pint of blood mixed with stomach contents. She was immediately rushed to the hospital and by 2:30 A.M. had passed an obvious melena stool.

Physical examination: Patient looked anemic and restless. She was stout and there was no sign of loss of weight. Temperature was subnormal and her pulse was 130 per minute and of a low volume. Blood pressure was 130/70.

Abdominal inspection revealed nothing special. The liver was enlarged about one finger, the spleen was not palpable. There was a tumor the size of a table tennis ball in the right axillary line in the region of the liver. This swelling moved with respiration, and it was thought to be a palpable gall bladder. The patient was slightly tender over the liver area. There were no dilated veins over the abdomen. A rectal examination was negative. Apart from a soft systolic murmur at the apex of the heart all the systems appeared quite normal.

Provisional diagnosis: Bleeding from a gastric ulcer or esophageal varices.

The patient was given three pints of blood but in spite of that her condition did not improve and although the washings from the Levin tube in the stomach were clean for short periods she continued to vomit large quantities of bright red blood about every half hour.

After another two pints of blood, and with blood still running in fast she was taken to the operating room. Her blood pressure was now 110/60.

Operation: A right paramedian incision was made and after a quick preliminary examination of the other organs, which appeared normal except for a large gall bladder full of stones, the stomach and duodenum were carefully examined. No lesion could be seen or felt. The lesser sac was opened, the stomach palpated between both hands and the posterior wall of the stomach inspected.

Again no abnormality could be detected. The stomach was then opened by a wide gastrotomy incision and a small ulcer with a spurting vessel was seen in the region of the greater curvature near the middle third of the stomach. The bleeding vessel was controlled by a stitch. The ulcer was about 1 cm. in diameter and looked macroscopically very much like an acute ulcer.

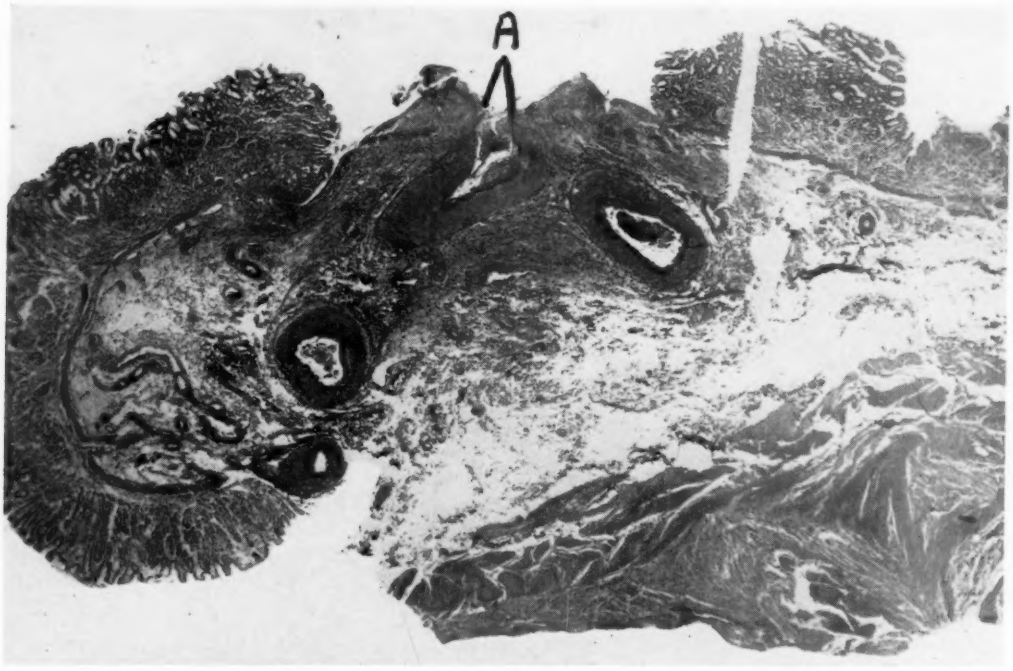

Fig. 3.—Whole thickness of stomach wall. Superficial ulcer with, at (*A*), an artery with obvious rupture. Other arteries show endarteritis. (×12; reduced ⅙.)

A partial gastrectomy was done including the ulcer area. As the patient was old and her condition weak, nothing was done to the gall bladder.

The patient received another transfusion of 500 c.c. of blood on the second postoperative day as she still appeared to be anemic.

The patient developed acute cholecystitis in the postoperative period, and was severely ill. This attack subsided slowly and delayed her recovery, so that she was discharged from hospital on the thirty-third postoperative day.

Pathologist's report: The specimen consisted of a large part of the stomach, and a small portion, received separately, which had been removed from the middle third of the greater curvature. The smaller portion contained a superficial ulcer, 1 cm. in diameter, the floor of which was covered with necrotic material and fibrin.

Sections showed a superficial peptic ulcer with microscopic features very similar to the second case (Fig. 3). The ulcer was superficial and extended only to the submucosa. An artery, 0.9 mm. in diameter, was partially filled with a fibrin plug. Neighboring arteries showed reactive endarteritis.

The mucosa, a few millimeters away from the artery, was 2.0 mm. in thickness and showed chronic gastritis changes of the same type as in Case 2.

Histologic diagnosis: Acute peptic ulcer with erosion of an artery. A moderate degree of chronic gastritis was also present.

DISCUSSION

Taylor and Strange[1] have recorded their experience with acute gastric ulcers, and have invited others to confirm their findings.

We have recorded three cases which we feel fall into the category of primary acute gastric ulcer. The cases were all seen within the compass of one week end during our emergency duty period at the General Hospital, Pretoria.

The clinical features and operative findings differ somewhat from those described by Taylor and Strange.

a. Only one ulcer occurred high on the lesser curve. One was on the posterior wall, and the one on the *anterior* wall, near the *greater* curvature.
b. The ages of our patients were 69, 70, and 75, respectively—much older than the average age in Taylor and Strange's series.
c. The diameter of one of the ulcers was 2 cm., i.e., greater than in Taylor and Strange's series.

We have confirmed that these ulcers cause massive, almost uncontrollable hematemesis, and also that the history of the illness is very short.

We wish to emphasize that the situation of the ulcers could not be determined by external inspection and palpation of the whole of the stomach. Only by a large gastrotomy could the entire inner surface of the stomach be inspected and the bleeding ulcer located. We, therefore, prefer a gastrotomy followed by gastrectomy, to a "blind gastrectomy."

If a blind gastrectomy had been done, the ulcer in Case 2 would have been left in the gastric pouch.

For those who perform a "blind gastrectomy," however, we would point out that a gastrectomy should not really be "blind."

The gastric pouch should be opened for inspection, and so should the duodenum, before completing the procedure.

SUMMARY

1. Three cases of massive gastric hemorrhage from acute ulcers are reported.

2. The ulcers occurred on the lesser curvature, posterior wall, and the greater curvature, respectively.

3. The history in all cases was brief.

4. Location of the bleeding ulcer at operation was impossible until a large gastrotomy allowed inspection of the mucosa of the stomach.

5. We do not favor "blind gastrectomy" in this type of case. If "blind gastrectomy" is performed, the gastric pouch, and the duodenum, should be opened for inspection and palpation, before completing the procedure.

The photomicrographs illustrating this article were taken by means of a Vickers projection microscope supplied by the South African Council for Scientific and Industrial Research.

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DUODENAL ULCER AND THE HYPOPHYSIS-ADRENAL STRESS MECHANISM

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IN A series of over eleven hundred duodenal ulcer patients studied in this clinic, the fasting nocturnal secretion of gastric juice has been regularly found to be from three to twenty times greater than that found in normal people. A hypersecretion of gastric juice of this degree if reproduced in experimental animals consistently produces progressive peptic ulcers in the duodenum. Complete division of the vagus nerves to the stomach has been found to abolish this hypersecretion dependably, and, if the operation is combined with an adequate pyloroplasty or a gastroenterostomy with the stoma located in the antrum close to the pylorus, the ulcers have usually been found to heal and remain healed. These observations have led to the conclusion that duodenal ulcers are caused and maintained by a hypersecretion of gastric juice and that this hypersecretion is of nervous origin and is due to a continued bombardment of the gastric glands by impulses in the vagus nerves. It is attractive to speculate that in some way the stresses and strains of modern life produce this secretory hypertonus in the vagus nerves and that it is in this way that the central nervous system plays its role in the genesis of duodenal ulcer.

Recent reports, however, have drawn attention to another possible pathway in the control of gastric secretion and the formation of peptic ulcer.[4, 5] While accepting the anterior hypothalamic-vagus mechanism as the mediator of the ordinary cephalic phase of secretion, these investigators[4, 13] have implicated the posterior hypothalamic-pituitary-adrenal cortical mechanism as a cause of hypersecretion of acid gastric juice in stressing situations. The posterior hypothalamus is visualized as the receptor of physical stress stimuli via the epinephrine released from the adrenal medulla, and of mental stress stimuli by direct nervous connection from the cerebral cortex. The hypothalamus then transmits these stimuli to the anterior pituitary which in turn releases ACTH. Corticotropin, subsequently, causes the adrenal cortex to secrete excessive amounts of cortisone. Cortisone, the end product of this series of reactions, then acts directly on the gastric glands inducing a hypersecretion of acid. Thus, two cephalic mechanisms are said to be involved, one "vagal" and one "extravagal."

The origin of this theory lay in the following experiments. Using monkeys for test animals and collecting gastric secretion samples by Levin tube, artificially induced stressed states were produced by injecting insulin, epineph-

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rine, cortisone, and ACTH at different times. The following was reported: ACTH, given to normal animals, caused a secretion of acid in two to three hours. This response was prevented by adrenalectomy. Similarly, cortisone, given to normal animals, caused a secretion of acid in the same period which could not be prevented by vagotomy.

When insulin was given to a normal animal, a biphasic curve was described, the initial secretory response being the vagal secretion at one to two hours and a second response occurring at three to five hours being caused by the extravagal (hypothalamic-pituitary-adrenal cortical) mechanism. The two cephalic mechanisms are noted to be independent because vagotomy prevents the first response and adrenalectomy prevents the second, thus leaving the stomach of a vagotomized adrenalectomized animal totally unreactive to insulin injection. Evidence is presented that the extravagal response of the stomach is initiated by the peripheral release of epinephrine which then stimulates the hypothalamus to set in motion the pituitary-adrenal cortex mechanism.

Opposed to this attractive hypothesis are the following reports: The intravenous insulin test has long been used as a test for the presence of vagal fibers to the stomach. Ordinarily the test was terminated in a two-hour period because the maximum response was expected in one and one-half hours. Rowe and associates[14] have studied insulin tests with prolonged collections (five hours) in duodenal ulcer patients before and after vagotomy. Their data show that a sizable number of patients not operated upon, as well as those showing a response to insulin after surgery, produced the most acid during the last three hours of collection. They did not report a trend of early responses in one to two hours and delayed responses in three to five hours during the same tests.

The concept that the delayed gastric response to insulin is caused by a release of epinephrine, which is necessary to discharge the pituitary-adrenal mechanism, must also be examined. Sayers[16] contends that, while there is a common association of sympathoadrenal (medulla) and pituitary-adrenocortical activity in response to stress, there is no substantial evidence that epinephrine acts on the adenohypophysis or adrenal cortex and could lead to the increased secretion of adrenal cortical hormones. Similarly, Thorn[19] and others[7, 8, 15] have reported that, while epinephrine precipitates a fall in the eosinophil count, it does not result in stimulation of the adrenal cortex.

Finally, from direct studies of gastric secretion in pouch dogs, it is well documented that sympathectomy increases gastric secretion.[11, 18] Hence, it would appear that epinephrine should inhibit gastric secretion. Baronofsky and Wangensteen[1] found that Pavlov and Heidenhain pouch dogs did not secrete in response to injection of aqueous epinephrine.

The question of the gastric secretory effect of ACTH and cortisone is still open. Gray and associates,[5] in reporting a high incidence of exacerbation of upper gastrointestinal ulceration following the use of ACTH, were the first observers to claim an associated hypersecretion of acid gastric juice. They felt, however, that repeated doses of ACTH for periods up to seven to fourteen days were necessary to initiate an increase in acid secretion. Four patients given oral cortisone showed no rise in acid secretion in a twenty-four-hour

period. Hirschowitz and associates[6] gave ACTH gel to six normal individuals and reported a relatively constant amount of acid secretion during a six-day test period in five subjects, but a marked rise in the sixth subject on the fourth day when evidence of duodenal ulceration appeared. A more constant finding was the decreased amount of mucus and viscosity.

Other investigators[3] have been unimpressed with the importance of the pituitary-adrenal cortical system in the majority of chronic duodenal ulcer cases with a high acid secretion. This belief is firmly based on the observation that vagotomy and a drainage procedure eliminate hyperacidity and cure 90 per cent of these patients without interfering with the pituitary-adrenal mechanism. Furthermore, large doses of ACTH and cortisone given to gastric pouch dogs over a three- to four-week period do not result in an increase of acid secretion to the degree which has been found necessary to cause ulceration in the experimental animal.[20, 21]

It is not a simple matter to explain the linking of stressing stimuli (such as exposure to cold, anoxia, and the repeated injection of epinephrine[12] in animals), and gastrointestinal ulceration and hemorrhage in man and experimental animals which has been pointed out by Selye.[17] He has denied, however, the association of this phenomenon with excessive reaction of the pituitary-adrenal system because hypophysectomized and adrenalectomized animals are much more susceptible to the development of ulcers as a result of stressing circumstances.

Also of great interest, but difficult to interpret, are the recent statistical analyses of post-mortem records which reveal a rather high incidence of acute gastrointestinal lesions in patients dying following neurosurgical procedures.[2] A similarly increased incidence of gastrointestinal ulceration has been noted in patients succumbing to any major catastrophe, including burns, fractures, and myocardial infarction.[9, 10] While it has been widely asserted that the ulcerations are caused by excessive stimulation of the pituitary-adrenal mechanism, it has yet to be established that these conditions are accompanied by an immediate increase of the acid secretion of the stomach.

In view of the contradictory evidence presented, it seemed advisable to repeat and modify some of the crucial experiments outlined by French and associates.[4] In this study Heidenhain pouch dogs were used in which consistent, quantitative, uncontaminated gastric secretion specimens could be obtained. Such a pouch, being isolated and denervated, is ideal for the study of the secretory effect of humoral mechanisms. The stimuli given to the pouch dogs were insulin, epinephrine, ACTH, cortisone, hydrocortisone, and histamine.

METHODS AND RESULTS

Heidenhain pouch dogs which appeared in good health and secreted copiously when eating or injected with histamine were used as test animals. In all studies the secretions were collected in rubber balloons attached to the stainless steel cannulae. The volume was measured and the free acid was titrated with 0.1 N NaOH to the Topfer's reagent end point (pH 4.0). All data are given in milliequivalents of HCl (meq. = vol. in liters × clinical units of free

acid). The dogs were fasted during the night preceding the testing so that their control secretions contained little or no acid and any change could be ascribed to the test substance.

A. *Insulin Stress Tests.*—

1. *Regular dose insulin tests:* Four dogs were tested a total of seven times using 10 to 20 units of regular insulin* intravenously. This dose is usually sufficient to reduce the blood sugar to 20 to 30 mg. per cent. Secretions were collected for 7 to 9 hours in anticipation of the "delayed response" reported by French.[4] No significant responses were seen. (The slight responses seen in Dog No. 984 were very small and another test showed no acid at all.)

TABLE I. SECRETORY RESPONSE OF HEIDENHAIN POUCH DOGS TO A REGULAR DOSE OF INSULIN I.V. (MEQ. OF HCl)

	972	983	983	984	984	992	992
1 HR. CONTROL	0	0	0	0	0	0	0
UNITS OF REG. INSULIN	15	15	15	10	15	20	15
1 hour	0	0	0	0	0.0	0	0
2 hours	0	0	0	0	0.0	0	0
3 hours	0	0	0	0	0.0	0	0
4 hours	0	0	0	0	0.09	0	0
5 hours	0	0	0	0	0.0	0	0
6 hours	0	0	0	0	0.05	0	0
7 hours	0	0	0	0	0.0	0	0
8 hours	0	0	0		0.05		0
9 hours	0		0		0.02		0

2. *High dose insulin tests:* Although it has been observed many times that 10 to 20 units of insulin lowers the blood sugar and produces mild distress in both animals and man, it seemed reasonable to increase the stress inflicted on the animals by greatly increasing the dose of insulin. Accordingly, four dogs were given 100 units of regular insulin intravenously as this was found to be close to the maximum safe dose. Blood sugars were drawn every two hours until restored to control levels. Gastric secretions were followed for twenty-four hours.

TABLE II. SECRETORY RESPONSE OF HEIDENHAIN POUCH DOGS TO A HIGH DOSE OF INSULIN I.V. (MEQ. OF HCl)

	DOG NO. 999	BLOOD SUGAR (MG. PER CENT)	DOG NO. 1000	BLOOD SUGAR (MG. PER CENT)	DOG NO. 3	BLOOD SUGAR (MG. PER CENT)	DOG NO. 7	BLOOD SUGAR (MG. PER CENT)
1 HR. CONTROL	0	80	0	64	0	63	0	59
UNITS OF REG. INSULIN	100		100		100		100	
1 hour	0	55	0	32	0	21	0	5
2 hours	0		0		0		0	
3 hours	0	38	0	10	0	22	0	20
4 hours	0		0		0		0	
5 hours	0	28	0	39	0	10	0	22
6 hours	0		0		0		0	
7 hours	0	57	0	68	0	59	0	55
8-9 hours	0		0		0		0	
24 hours	0		0		0		0	

*Eli Lilly and Company.

In spite of the maximum stress produced by the large dose of insulin as evidenced by marked weakness and lethargy, as well as the depression of blood sugar to from 5 to 28 mg. per cent,* no secretion of acid occurred.

B. *Epinephrine Stress Tests.*—Three dogs were given large doses of epinephrine (3 mg.) subcutaneously as a stressing stimulus. Secretions that were followed for twenty-four hours revealed no acid.

TABLE III. SECRETARY RESPONSE OF HEIDENHAIN POUCH DOGS TO A HIGH DOSE OF EPINEPHINE (MEQ. OF HCl)

	1000	1000	3	999
1 HOUR CONTROL	.12	0	0	0
3 MG. EPINEPHRINE SUBCUTANEOUSLY				
1 hour	0	0	0	0
2 hours	0	0	–	0
3 hours	0	0	–	0
4 hours	0	0	0	0
5 hours	0	0	0	0
6 hours	0	0	0	0
24 hours	0	0	0	0

C. *ACTH Stress Tests.*—To continue evaluating the steps involved in the extravagal chain reaction leading to gastric secretion, ACTH (Wilson's Corticotropin, 40 U.S.P. units per cubic centimeter) was injected subcutaneously in 4 dogs. Doses of 40 and 80 units were used. Since the maximum effect of ACTH appears in about two hours, one would have expected the acid secretory response shortly after that time. The data revealed no significant acid secretion in the twenty-four-hour observation period.

TABLE IV. SECRETORY RESPONSE OF HEIDENHAIN POUCH DOGS TO AN INJECTION OF ACTH (MEQ. OF HCl)

	999	1000	1000	999	974	24
1 HOUR CONTROL	0	0	0	0	0	0
	40 UNITS ACTH SUBCUTANEOUSLY		80 UNITS ACTH SUBCUTANEOUSLY			
1 hour	0	0	0	–	0	0
2 hours	.06	0	0	0	0	0
3 hours	0	0	0	0	0	0
4 hours	0	0	0	0	0	0
5 hours	0	0	0	–	0	0
6 hours	0	0	0	0	0	0
7 hours	0	0	.05	0	0	0
24 hours	0	0	–	–	0	–

D. *Cortisone and Aqueous Hydrocortisone*† *Stress Tests.*—The final end product of the pituitary adrenal cortex mechanism, i.e., cortisone and hydrocortisone, were injected to complete the study.

1. Two hundred milligrams of cortisone (Schering) was injected intramuscularly into four dogs.

Free acid was completely absent from the collections except for the overnight secretions of D-1000. The experiment was repeated in this dog with

*Blood sugar determinations done by the Somogyi-Shaffer-Hartman method.

†Cortef, Hydrocortisone dissolved in alcohol (The Upjohn Company) produced a marked rise in secretion which was exactly equaled by an equivalent amount of ethanol given intravenously. Hence, an aqueous form was sought and was generously furnished by The Upjohn Company.

200 mg. cortisone with the same result and then a third time for control without cortisone—again with identical results. It was assumed from this that the secretory effect noted was not due to the cortisone, but that probably the dog had ingested feces and thus received the stimulation.

TABLE V. SECRETORY RESPONSE OF HEIDENHAIN POUCH DOGS TO AN INJECTION OF CORTISONE (MEQ. OF HCl)

	999	999	992	3	1000
1 HR. CONTROL	0	0	0	0	0
200 MG. CORTISONE INTRAMUSCULARLY					
1 hour	0	.02	0	0	0
2 hours	0	0	0	0	0
3 hours	0	0	0	0	0
4 hours	0	0	0	0	0
5 hours	0	0	0	0	0
6 hours	0	0	0	0	0
7 hours	0	–	0	–	–
24 hours	0	0	0	0	1.1

2. Aqueous Hydrocortisone (Sodium-hydrocortisone succinate)* was injected intravenously in an amount (66.8 mg.) equivalent to 50 mg. of hydrocortisone in five dogs for seven individual tests.

TABLE VI. SECRETORY RESPONSE OF HEIDENHAIN POUCH DOGS TO AN INJECTION OF AQUEOUS HYDROCORTISONE (MEQ. OF HCl)

	1000	999	999	24	24	40	40
1 HOUR CONTROL	0.0	0.0	0.0	0.0	0	0	0
50 MG. HYDROCORTISONE INTRAVENOUSLY							
1 hour	0.0	0.24	0.0	0.18	0	0	0
2 hours	0.0	0.07	0.0	0.64	0	0	0
3 hours	0.0	0.0	0.04	0.09	0	0	0
4 hours	0.0	0.0	0.04	0.02	0	0	0
5 hours	–	–	0.0	–	0	–	0
6 hours	–	–	0.0	–	0	–	0
24 hours	0.27	–	–	0.0	0	0	0

A mild response was shown on one occasion by one dog (D-24) which did not appear when the dog was retested a few days later.

E. *Histamine Tests.*—In order to prove that these animals were capable of responding to secretory stimuli, they were given an injection of 1 mg. of histamine base subcutaneously for comparison to the "stressing" stimuli.

Large volumes with high free acid concentrations resulted in each case.

TABLE VII. SECRETORY RESPONSE OF HEIDENHAIN POUCH DOGS TO AN INJECTION OF HISTAMINE (1 MG.) (MEQ. OF HCl)

	983	984	992	999	1000	3
1 HOUR CONTROL	0.03	0.0	0.0	0.0	0.0	0.0
1 MG. HISTAMINE SUBCUTANEOUSLY						
2 hour period	3.78	3.19	4.40	2.30	1.28	1.68

*Furnished by The Upjohn Company.

DISCUSSION

The data secured in these experiments, in which Heidenhain pouch dogs were given large doses of insulin, epinephrine, ACTH, cortisone, and hydrocortisone to evaluate the extravagal pathway of secretion, tend to confirm the doubts presented earlier about the validity of this mechanism.

If the extravagal mechanism did operate, one would have expected the Heidenhain (isolated denervated) pouch to give a delayed or extravagal response three to five hours after the insulin injection. This did not occur even with the massive 100 unit stressing dose of intravenous insulin.

Second, if peripheral release of epinephrine were necessary in the activation of a pituitary-adrenal-gastric secretion reaction, one would anticipate that the massive doses of epinephrine would have caused acid secretion, which they did not.

Again, if the above initiating stimuli were to discharge the anterior pituitary adrenal mechanism and cause gastric acid secretion, certainly the injection of ACTH would cause an acid reaction, which was absent.

Finally, cortisone and hydrocortisone, the end products of the series of reactions outlined above, cause no secretion of acid. Therefore, one must look for an explanation to the diametrically opposed data reported in this laboratory and that of French and associates.[4]

The experiments differed in the following ways:

1. Gastric secretion samples were collected from an isolated pouch through a cannula in this laboratory rather than through a Levin tube. In the former case, the sample is pure gastric juice, whereas, in specimens taken from the intact stomach, regurgitation of duodenal contents with the resultant change in pH of the sample plus the possibility of antrum stimulation cannot be ruled out as added variables affecting the data.

2. In the experiments reported here, both volume and free acid were measured, giving a quantitative measure of the amount of acid secreted in a given period. The data reported by French indicate that only pH was determined on the sample and volume studies were not done.

3. Our animals were tested while awake, whereas those of French were anesthetized.

4. Finally, the difference in experimental animal species (monkeys vs. dogs) is a variable whose importance can only be determined by further experimentation.

One must conclude from the data presented in our experiments that the exacerbation of peptic ulcer produced by ACTH and cortisone is probably not a result of increased gastric acid secretion.

SUMMARY

1. The evidence for and against an "extravagal" cephalic phase of gastric secretion involving the pituitary-adrenal axis and activated by extraordinary stressing stimuli is reviewed.

2. In an effort to evaluate the gastric secretory response to stress, Heidenhain pouch dogs were given massive doses of insulin, epinephrine, ACTH, cortisone, and hydrocortisone. The acid secretions were followed for twenty-four hours.

3. The data collected indicate that acid secretion from an isolated denervated pouch is not stimulated by the above listed agents in a twenty-four-hour period.

4. On the basis of these experiments, there is no evidence to substantiate the theory that hypersecretion of acid and ulcer formation are a result of overstimulation of the pituitary-adrenal cortex mechanism.

5. The exacerbation of peptic ulcer produced by ACTH and cortisone is probably not a result of increased gastric acid secretion.

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INTRATHORACIC ENTEROGENOUS ANOMALY COMMUNICATING WITH THE SMALL INTESTINE

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CERTAIN intrathoracic enterogenous anomalies have been designated by a variety of terms, including "mediastinal cyst," "enterogenous cyst," "enteric cyst," "enterocystoma," "cysts of foregut origin," "archenteric cysts," and "duplications of the alimentary tract." Since all of these anomalies take origin from the foregut, they are all enterogenous in nature and we prefer to use the term "enterogenous" for their designation.

These enterogenous anomalies may assume various forms. They may be spherical and cystic, in which case the term "enterogenous cyst" is appropriate. A further subdivision of this group of enterogenous cysts might be made, depending on the microscopic appearance of the lining and the wall of the cyst, such as esophageal or gastric.

A second group of such anomalies are those elongated tubular structures that resemble a portion of the gastrointestinal tract in external appearance. Their lining mucous membrane is similar to some portion of the alimentary tract and they may be separate from, attached to, or communicating with a portion of the alimentary canal. Anomalies of this type have been referred to in the literature as "duplications of the alimentary tract."

We wish to report an unusual case of an intrathoracic duplication communicating with the small intestine that was removed successfully from a 3½-month-old child. Reports of 11 other cases of a similar nature have been found in the medical literature.

REPORT OF CASE

A white boy, 3½ months of age, was brought to the Mayo Clinic in July, 1955, because of anemia, watery stools, and projectile vomiting.

Present Illness.—The child had appeared pale and anemic since birth. An iron preparation had been administered for the three weeks preceding admission and the child's stools soon thereafter became black and watery. A period of constipation followed. Projectile vomiting commenced three days before admission.

Past History.—The child had had a normal delivery and was born three weeks prematurely. He had been examined at the clinic when he was six weeks of age because of a swelling in the sacral region, which was considered to be a dermal cyst. A thoracic roentgenogram was interpreted as demonstrating multiple pneumatoceles of the right lung.

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The ribs on the right showed minor anomalies, and an anomaly of the upper thoracic portion of the spinal column was noted, with faulty segmentation and incomplete closure of the neural canal.

Examination.—The child was extremely pale. The spleen was barely palpable. The dermal cyst in the sacral region was unchanged.

Laboratory.—The value for hemoglobin was 3.2 Gm. per 100 ml. of blood. The erythrocyte count was 1,600,000 cells per cubic millimeter of blood and the leukocyte count was 13,000. Stained smears of the blood showed hypochromasia, some polychromasia, chromatin rests, normal platelets, and an increased number of monocytes. Cellular immaturity was not present. Cultures of stools revealed normal flora.

A thoracic roentgenogram was interpreted as demonstrating right pleural effusion with loculation. Air spaces again were noted in the region of the right lower lobe (Fig. 1).

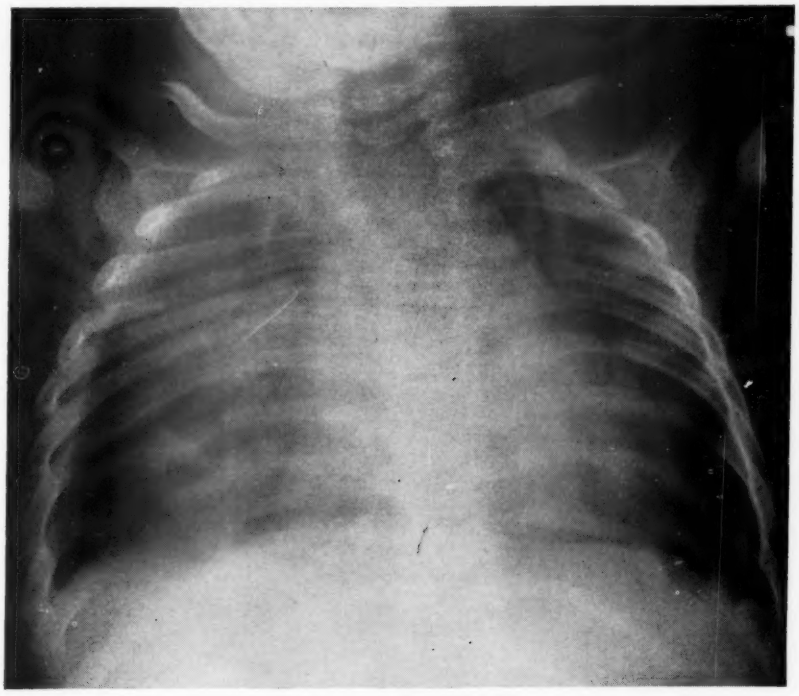
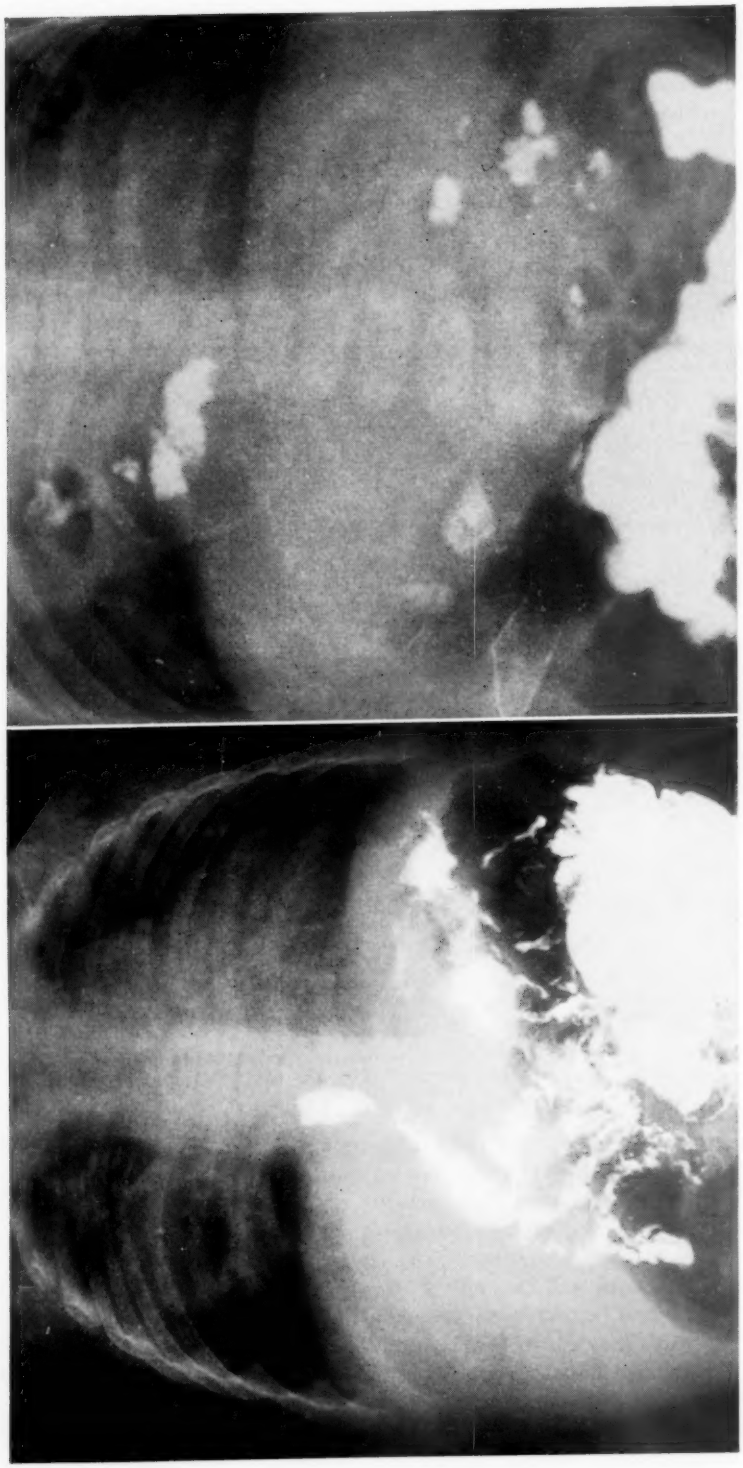


Fig. 1.—Abnormal air-filled spaces are noted in the region of the right lower lobe. Faulty segmentation and incomplete closure of the neural canal are present in the lower cervical and upper thoracic portions of the spinal column.

Course.—Supportive measures, including blood transfusions, were instituted; the value for hemoglobin increased to 12 Gm. A tentative diagnosis of congenital lobar emphysema of the right lower lobe with possible complicating empyema was made, and an antibiotic program was outlined. It became apparent, however, that the black stools persisted, although use of the iron preparation had been discontinued. Because of the known association of spinal and enterogenous anomalies, a diagnosis of intestinal duplication with ulceration and hemorrhage was considered and roentgenograms of the small intestine were made. They were interpreted as demonstrating a diaphragmatic hernia (Fig. 2). A preoperative diagnosis of diaphragmatic hernia was made and surgical treatment was advised.

Operation.—A posterolateral incision was made on the right and the thorax was entered through the seventh intercostal space. A large mass was found lying posteromedially. It was densely adherent to an otherwise normal right lower lobe. Dissection revealed the mass to be composed of what appeared to be small intestine. Ulceration was



B.

A.

Fig. 2.—Roentgenograms of the small intestine showing the barium-filled intestine extending from the abdomen into the right hemithorax.

present, with perforation of the mass onto the basilar segments of the right lung. A single limb of intestine passed into the abdomen through the right side of the aortic hiatus. This was transected at as low a level in the thorax as possible and the inferior limb was oversewn. The mass was then separated from the lung. The only attachment remaining then was the blood supply, which came directly from the diaphragmatic vessels, the adjacent mediastinal vessels, and the aorta itself. These vessels were divided and the mass was removed. The thorax was closed in layers after temporary drainage by means of an intercostal tube was instituted.

Fig. 3.—Opened surgical specimen. Gastric mucosa with peptic ulceration is present on the right. A small probe passes beneath a mucosal bridge.

Pathologic Appearance.—The specimen measured 12 cm. in length and 2 cm. in width (Fig. 3). Examination revealed duplication of the intestine grossly resembling small intestine. The distal third was lined by gastric mucosa and contained a perforating peptic ulcer 1 cm. in diameter that was associated with a considerable degree of inflammation and fibrosis. The mid-portion of the duplication was double-barreled for a distance of 4 mm. There were no "skip areas" of gastric mucosa; all of it was in one patch adjacent to the ulcer. A short distance from the gastric mucosa was found mucosa resembling that seen in the distal two thirds of the duodenum; the mucosa near the resected end was characteristic of that found in the normal ileum.

Postoperative Course.—The child made an uneventful recovery. The intercostal tube was removed on the second day after operation and he was dismissed home after fourteen days.

He returned five months later, at which time his general condition was excellent. Another intestinal roentgenogram was made in an attempt to demonstrate the point of origin of the abdominal portion of the intestinal duplication. This roentgenogram was interpreted as normal.

COMMENT

Excellent reviews of the subject of alimentary duplications have been made by Fallon and associates[5] and by McLetchie and co-workers.[13]

The degree of intimacy between duplications and the alimentary tract varies greatly. Some duplications cannot be separated from the adjacent intestine while maintaining the integrity of the latter. In the case of Owen and associates,[14] the duplication was overlooked at two previous laparotomies. At the third operation, the stomach appeared grossly normal. The duplication was readily apparent when the stomach was palpated carefully. Excision of

TABLE I. SUMMARY OF REPORTED CASES OF INTRATHORACIC ENTEROGENOUS ANOMALIES COMMUNICATING WITH THE ALIMENTARY TRACT

AUTHOR	CASE	DATE	SEX	AGE AT ONSET OF SYMPTOMS	SYMPTOMS	SPINAL ANOMALIES	AGE AT OPERATION	ORIGIN AND COURSE OF ANOMALY	SURGICAL PROCEDURE	TYPE OF MUCOSA PRESENT	ULCERATION	RESULT
Case records of the Massachusetts General Hospital[2]	1	1950	M	Birth ?	Cough, vomiting, failure to gain weight	Yes	4 mo.	Upper jejunum; right diaphragm and right thorax	Excision of supradiaphragmatic portion only	Esophageal, small intestinal	No	Died
Gross and associates[9]	2	1950	F	2 mo.	Vomiting, cyanosis, dyspnea	Yes	3½ mo.	Upper jejunum; right diaphragm, right thorax, left thorax	Excision of supradiaphragmatic portion only	Jejunal, colonic, respiratory?	No	Good
	3	1950	M	2 mo.	Anemia, tarry stools	Yes	4 mo.	Upper jejunum; posterior diaphragm, right thorax	Total excision	Gastric, duodenal (pancreatic)	No	Good
	4	1950	M	3 yr. ?	Feeding problem, back pain	?	4 yr.	First portion of duodenum; right crus, right thorax	Excision, leaving small portion on duodenum	Gastric	No	Good
Van der Hal and Mooy[16]	5	1950	F	6 mo.	Anemia, tarry stools	?	6 mo.	Ileum; right thorax	None	Gastric	Yes	Died
Fisher[7]	6	1950	M	3½ mo.	Pallor, tarry stools	Yes	5 mo.	Ileum; right diaphragm, right thorax	Total excision	Gastric, jejunal	Yes	Good

Davis and Barnes[3]	7	1952	F	2 wk.	?	Abdominal pain, tarry stools	Yes	5 yr.	Upper jejunum; central diaphragm, right thorax	Total excision	Gastric, esophageal	Yes	Good
Field[6]	8	1952	F	?		Tarry stools, dyspnea	Yes	2½ mo.	Lower jejunum; right thorax, left thorax	Excision, leaving small thoracic fragment	Gastric, small intestinal	?	Died
Owen and associates[14]	9	1954	F	4 yr.		Epigastric pain	?	25 yr.	Duodenum; central diaphragm, thorax?	Excision of abdominal portion	Gastric	No	Good
McLetchie and associates[13]	10	1954	M	4 mo.		Feeding problem, respiratory embarrassment, melena	Yes	8 mo.	Duodenum; central diaphragm, left thorax	Laparotomy	Gastric	Yes	Died
Leider and associates[11]	11	1955	M	6 mo.		Respiratory difficulty, vomiting, occult blood in stools	Yes	1 yr.	Jejunum; aortic hiatus, right thorax, left thorax	Total excision	Gastric, small intestinal	No	Good
Caruolo and associates (present case)	12	1956	M	Birth	?	Anemia, vomiting, tarry stools	Yes	3½ mo.	Upper small intestine; aortic hiatus, right thorax	Excision of thoracic portion	Gastric, duodenal, ileal	Yes	Good

the abdominal portion of the duplication, with anastomosis of the thoracic segment to the fundus of the stomach, required reconstruction of the greater curvature. Some duplications run parallel to the normal intestine but reasonably separate from it. Thoracoabdominal duplications, except when they have an attachment to the normal intestine, may run an independent course.

Duplications may be found exclusively in the thorax, where they communicate with the esophagus, as in the case of Hutchison and Thomson.[10] They are commonly found in the abdomen, where they may or may not have a communication with the lumen of the intestine.

Dickson and associates,[4] in 1946, reported the first successful removal of a thoracoabdominal duplication; however, it did not communicate with the alimentary canal. The first report of a duplication similar to the one described in our paper is that found in the case records of the Massachusetts General Hospital.[2] The first such lesion successfully operated on was that reported by Gross and co-workers.[9]

The salient features of the reported thoracoabdominal duplications communicating with the small intestine are presented in the accompanying table.

The average age at onset of symptoms was frequently less than one year, and treatment often followed within a matter of weeks. These duplications tended to arise from the proximal portion of the small intestine, to penetrate the right or central portion of the diaphragm, and to occupy a position in the right side of the thorax.

Gastric mucosa was found in 10 of the 12 cases. It always was present in the thoracic portion of these 10 duplications but did not always extend into the abdominal portion. Peptic ulceration occurred in one half of these 10 cases. Any type of mucosa normally found between the esophagus and the anus, inclusive, may be present. A respiratory type of mucosa occasionally is found. The external appearance of a duplication cannot be relied on as a guide to the nature of the mucosal lining. Van der Hal and Mooy[16] stated that the duplication in their case could not be distinguished from normal small intestine, yet it contained gastric mucosa. Ectopic pancreatic tissue may be present.

The blood supply comes from mesenteric vessels inferiorly, from vessels of the diaphragm and mediastinum, and directly from the aorta.

Symptoms and Diagnosis.—The symptoms produced by these anomalies fall into two general categories, namely, cardiorespiratory and alimentary. Both may be present in a patient. Cardiorespiratory symptoms are produced by the space-occupying capacity of the duplication and the resulting pressure on adjacent structures. They also may result from irritation due to peptic ulceration in the thorax. Alimentary symptoms also may be the result of pressure or they may be due to blood in the gastrointestinal tract. Secondary anemia from loss of blood is frequently present.

The diagnosis is suggested when compatible symptoms are accompanied by findings on thoracic roentgenograms consistent with a diaphragmatic hernia or so-called pneumatoceles. When typical anomalies of the spinal

column are found in addition, intrathoracic duplication should be regarded as the most likely diagnosis. If a connection with the small intestine is present, it may be manifested by blood in the stool or the appearance of barium in the "pneumatoceles" after ingestion of barium. The most important differential diagnosis obviously is between this lesion and diaphragmatic hernia; except for the association of duplications and spinal anomalies, it would be most difficult to distinguish one from the other.

Theory of Origin: Association With Spinal Anomalies.—Several theories of origin have been suggested for these unusual duplications. Early writers favored the idea that they represented remnants of the omphalomesenteric duct.[5] Lewis and Thyng[12] stated that tiny intraluminal diverticula may expand to produce the duplication, while Bremer[1] advanced the theory of faulty vacuolization of the alimentary tract. It is also possible that duplications may result from sequestration or pinching off of a group of cells from the primordial intestinal tube.[8]

The presence of spinal anomalies could not be excluded from the data presented in 3 of the 12 reported cases. Such anomalies were present in all of the remaining 9 cases. They are found in association with thoracic duplications whether or not a connection with the normal intestine is present. They are found in association with abdominal duplications only if the duplication extends into the thorax or is accompanied by an independent thoracic duplication.

This relationship between intrathoracic duplications and spinal anomalies has been known for some time. The first association between the two was established by Roth,[15] in 1881, in the very first publication on enteric cysts of the mediastinum. Fallon's group[5] and McLetchie and associates[13] recently have advanced a theory to explain the development of the associated spinal and enterogenous anomalies. They have shown how faulty excalation of the notochord may produce thoracic duplications and, simultaneously, spinal anomalies.

The notochord, which arises from mesodermal tissue lying between the ectoderm and the entoderm, comes to lie in close association with the entoderm during the course of development. The notochordal cells normally become excalated from the entoderm, which later forms the alimentary canal, and are enveloped by mesodermal cells, which later form the adult vertebral column. If the connection between notochord and entoderm is not lost, the notochordal cells may draw with them some of the adjacent entodermal lining, forming either a cyst lined by alimentary mucosa or a mucosa-lined pouch connected with the intestine. In addition, there is interference with the normal formation of the spinal column due to this traction of the entodermal cavity back into the mesoderm.

It appears reasonable that this process may explain some of the enterogenous anomalies found in the thorax. The question naturally occurs as to why

spinal anomalies are not found in association with purely abdominal duplications. Further study of the problem may reveal that they are present, at least temporarily, but do not persist beyond the fetal stage.

Because the "notochord" theory does not explain all duplications, it does not appear wise at this time to adopt it to the exclusion of those theories mentioned previously.

Treatment.—The definitive treatment of these unusual lesions is complete surgical removal. To accomplish this, it was necessary in several of the reported cases to carry out multiple operative procedures. A simple approach would be more satisfactory. Because of the location of the lesion in both abdomen and thorax, decision concerning the proper surgical approach is a difficult one. We believe that the thoracic portion of the duplication should be removed in each instance because of the presence in practically every lesion of gastric mucosa in this part of the duplication. The anomaly, then, should be approached primarily through the thorax. The entire thoracic portion may be excised. If the gastric mucosa is completely removed and histologic examination of the cut end of the duplication at the diaphragm shows intestinal rather than gastric mucosa, the abdominal portion may be left in situ after the open end is oversewn. If gastric mucosa extends into the abdominal portion of the duplication, it is essential that it be removed at the same operation, if possible. This may be accomplished by extending the incision into the abdomen as a thoracoabdominal incision, by making a separate abdominal incision or by making an incision in the flank, as suggested by Gross and associates.[9] Similarly, the abdominal portion of the duplication should be removed if gastrointestinal symptoms are prominent.

In our case, the cut end of the thoracic portion of the duplication showed mucosa typical of the small intestine, suggesting that the gastric mucosa had been removed completely. The subsequent uneventful course of the patient substantiated the opinion that the small remaining abdominal portion of the duplication is of no physiologic consequence.

SUMMARY

An unusual case of intrathoracic enterogenous anomaly communicating with the small intestine was encountered in a 3½-month-old boy. Surgical removal was accomplished through a posterolateral thoracic incision. The child made an uneventful recovery.

Survey of the literature disclosed reports of 11 similar cases. The salient features of the reported cases have been discussed.

Surgical excision is the treatment of choice. Total removal of that portion of the duplication lined by gastric mucosa is essential in the prevention of postoperative complications.

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THE EXAMINATION OF THE GASTRIC MUCOSA THROUGH A LARGE GASTROTOMY IN THE DIAGNOSIS OF INTESTINAL HEMORRHAGE OF OBSCURE ORIGIN

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THE surgeon who explores a patient with gastrointestinal bleeding of obscure origin is faced with a difficult problem when no abnormalities are found on palpation of the stomach and intestines. Several authors have reported that the performance of a so-called "blind" gastrectomy in the absence of demonstrable pathology will prevent recurrent hemorrhage in a significant number of patients.[2-6, 8-11, 13, 14] The success of blind gastrectomy may be due either to the removal of bleeding lesions which cannot be palpated through the gastric wall, or from healing of an ulcer as the result of reduction of gastric acidity. Some advocates of blind gastrectomy specifically recommend against preliminary gastrotomy, stating that it is unrewarding,[9] futile,[14] and "dirty."[10] The purpose of the present discussion is to present data to support the careful examination of the gastric mucosa through a large gastrotomy in patients on whom a blind gastrectomy is considered.

It is apparent from review of the current literature that failure to find the source of bleeding at laparotomy is a common occurrence. This was true in 6 of 18 patients reported by Cooper and Ferguson,[2] in 4 of 11 patients reported by Thieme,[14] in 5 of 11 by Gilchrist and Chun,[4] in 19 of 110 patients by Stewart, Massover, Potter, and Schaer,[12] and in 4 of 20 patients by Mayo and Owens.[8] It is well known that acute gastric erosions involving only the mucosal layer of the stomach wall may be the source of exsanguinating hemorrhage.[2, 3, 11, 13-15] Since these erosions do not penetrate the muscular wall of the stomach, they are not palpable by external examination. The performance of a blind subtotal gastrectomy in the hope that such erosions exist within the stomach is suggested by a number of authors. In contrast to those who do not employ preliminary gastrotomy, Amendola[1] strongly advised a gastrotomy to locate the bleeding point prior to gastric resection. Loe[7] has suggested inspection of the gastric mucosa through a sigmoidoscope inserted through the gastric wall. Gilchrist[4] reported 3 patients who underwent blind subtotal gastrectomy but died in the early postoperative period from bleeding ulcers left in the gastric remnant. He agreed with Amendola on the desirability of location of the bleeding point by gastrotomy before performing a gastric resection.

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TECHNIQUE OF GASTROTOMY

The success of gastrotomy in the patients reported here is in large measure due to thorough exploration of the interior of the stomach. The general surgical principles of adequate exposure, hemostasis, and good illumination that are followed in the exploration of the peritoneal cavity should also be followed in examination of the interior of the stomach. An adequate examination of the stomach requires a methodical inspection of

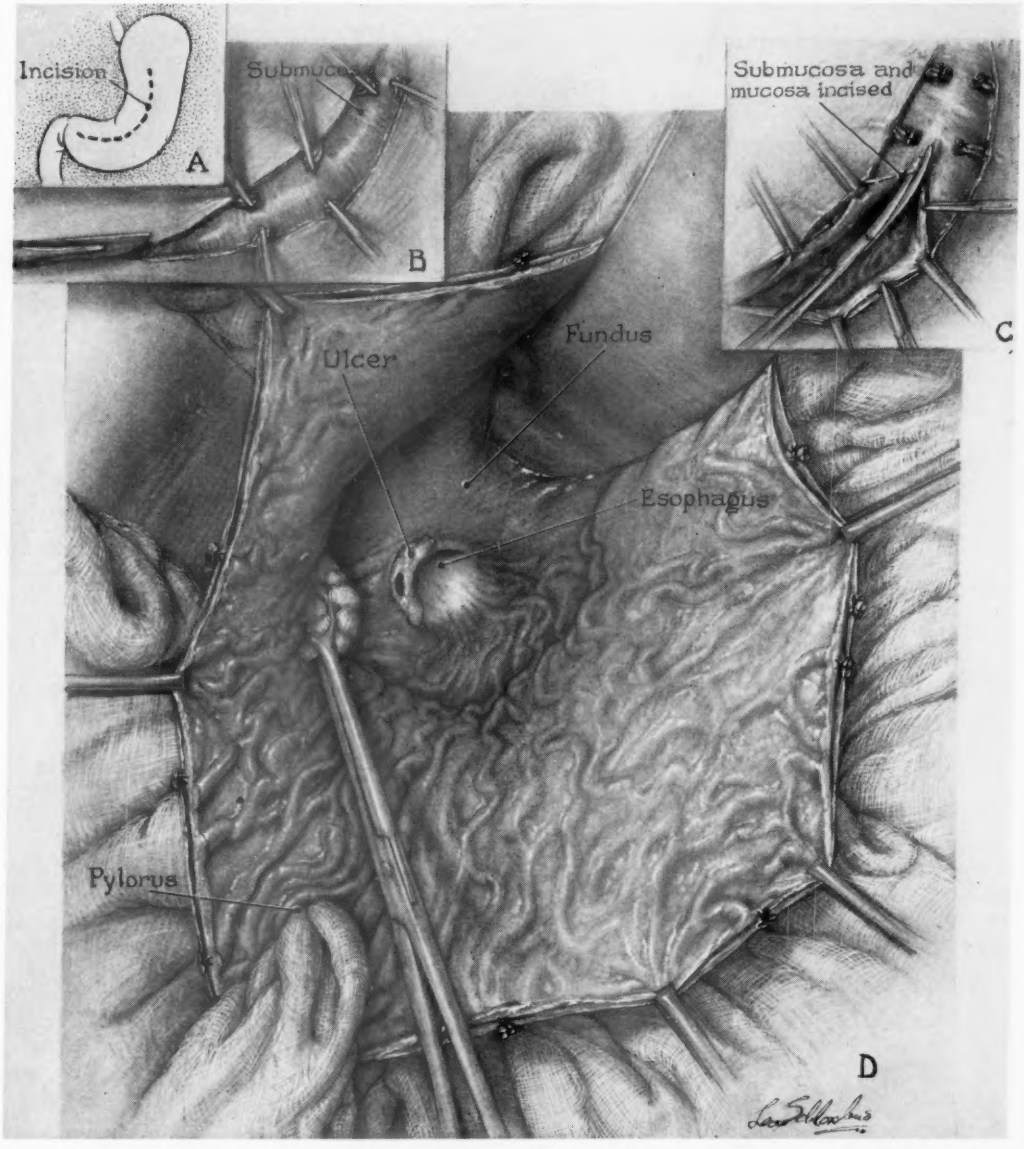

Fig. 1.—Technique of gastrotomy. *A*, incision; *B*, the submucosal bleeding points are clamped; *C*, mucosa is incised; and *D*, the exposure readily shows an ulcer at the esophagogastric junction with an eroded blood vessel in the base of the ulcer (Case 2).

the gastric mucosa from the esophagogastric junction to the pylorus. A small erosion may easily be hidden in the depths of a mucosal fold. Hence, an important point in inspection is the application of tension to various portions of the gastric wall so that the intervening folds of gastric mucosa are stretched into a smooth surface.

A longitudinal incision is made on the anterior surface of the stomach midway between the greater and lesser curvatures, beginning just proximal to the the pylorus. It

is extended upward for a distance of about seven inches (Fig. 1, *A*). The incision usually extends to the area where the stomach is transected in performing a 70 per cent gastric resection. The gastric wall is initially incised only to the submucosal layer (Fig. 1, *B*). Blood vessels are clamped and ligated in order to prevent bleeding into the stomach when the mucosa is incised. Bleeding points in the mucosa are ligated as the mucosa is incised (Fig. 1, *C*). The hemostasis obtained by this technique avoids the necessity of traumatizing the gastric mucosa at the edges of the gastrotomy incision by repeated sponging. The edges of the wound are grasped with Allis clamps and held apart while wide Deaver retractors are inserted. A finger is passed through the pylorus and a bimanual palpation of the first, second, and third portions of the duodenum is performed. The interior of the stomach is then examined from the pylorus upward to the highest portion of the cardia.

Fig. 2.—The gastric mucosa seen through a gastrotomy in a patient with a small sessile polyp that was difficult to palpate. The polyp lies to the right of the Levine tube projecting through the cardia.

The squamous-cell epithelium of the esophagus can be seen and the esophagogastric junction can be carefully inspected. Traction applied with sponge sticks to the gastric wall permits the obliteration of gastric rugae and visualization of the deepest crevices. The exposure obtained is illustrated in Figs. 1, *D* and 2. Fig. 1, *D* shows the ulcer found near the esophagus in Case 2. Fig. 2 shows a sessile polyp visualized within the stomach that had been palpated through the gastric wall. As this case was diagnosed prior to gastrotomy, it is not included in the case reports.

Saline solution irrigations and a portable spotlight may be helpful. Since a suction tip may traumatize gastric mucosa and initiate bleeding, suction is applied only through moistened gauze sponges. If no gastric lesion is encountered, a duodenotomy should be considered.

Soiling of the peritoneal cavity with gastric contents is minimized by placing gauze pads around the stomach before the gastrotomy is performed. Soiled instruments and gloves employed during the gastrotomy should be discarded after the incision in the stomach is closed.

CLINICAL MATERIAL

Eighteen patients were operated upon by the authors in a one-year period for previously undiagnosed gastrointestinal bleeding. In 7 of the patients, the bleeding area was located easily and a gastrotomy was not necessary. The remaining 11 patients form the basis of this report.

CASE 1.—V. W., No. 650933, a 56-year-old white woman, gave a five-year history of epigastric distress and recurrent gastrointestinal bleeding. Gastric analysis showed a histamine achlorhydria; no lesions were demonstrated on repeated x-ray studies with barium meals. An exploratory laparotomy was performed. External examination of the stomach and duodenum showed no abnormality. A large gastrotomy revealed two superficial gastric ulcers, each one centimeter in diameter, located high on the lesser curvature. The lesions did not extend into the muscularis and were not palpable even when their location was known. A 65 per cent subtotal gastrectomy was performed. The patient was doing well three months following surgery.

CASE 2.—E. B., No. 575231, a 58-year-old white man, was admitted for massive hematemesis and melena for the preceding twenty-four hours. He had had no previous symptoms referable to the digestive tract. There was a twenty-year history of chronic alcoholism, and the patient had been told that he had "hardening of the liver." Liver function studies were normal. An esophagoscopy showed no abnormalities. An x-ray examination with a barium meal showed a small hiatus hernia. A total of 7,500 ml. of blood was given in the first twenty-four hours in the hospital. Surgical exploration was then performed. A small hiatus hernia was the only lesion that could be found in the gastrointestinal tract. Palpation of the hiatus hernia showed no evidence of ulceration. A large gastrotomy was performed. There was a 10 mm. by 7 mm. ulcer at the junction of the esophageal and gastric mucosa. A small blood clot occluded an eroded artery located in the base of the ulcer. The ulcer was biopsied and the bleeding point transfixed with sutures. The gastrotomy was closed and repair of the hiatus hernia performed. The biopsy specimen showed the changes of acute and chronic inflammation on microscopic examination. The patient has had no recurrence of bleeding seven months following surgery.

CASE 3.—C. W., No. 114715, a 62-year-old Negro man, had had three episodes of massive gastrointestinal hemorrhage in the previous year. He had had both melena and hematemesis. There was infrequent epigastric discomfort relieved by bicarbonate of soda. Four separate x-ray studies revealed no pathology in the gastrointestinal tract. The gastric secretions on two separate determinations contained no acid after histamine stimulation. At laparotomy, palpation of the stomach and duodenum showed no abnormality. Examination of the remainder of the abdomen was also negative. A large gastrotomy revealed two small erosions about 4 mm. in diameter in the distal portion of the stomach that were actively oozing blood. Several other smaller erosions were seen in the mid-portion of the stomach about 7 cm. from the esophagus. None of these penetrated into the gastric wall. These lesions might have been missed by a "blind" gastrectomy. A high subtotal gastrectomy was performed. The patient was asymptomatic seven months after surgery.

CASE 4.—C. H., No. 693637, a 55-year-old white man, was admitted because of hematemesis and melena of several days' duration. The hematocrit was 13 per cent. He had had vague epigastric distress for several months. An x-ray examination with a barium meal was negative. Surgical exploration was done twenty-four hours after admission because of repeated hematemesis. A total of 4,500 ml. of blood had been given at this time. The stomach was distended with blood but contained no palpable abnormality. A large gastrotomy revealed a 4 cm. gastric ulcer on the lesser curvature in the upper third of the stomach. Blood was spurting from a vessel in the center of the ulcer. The ulcer

was removed with a 65 per cent subtotal gastrectomy that included most of the lesser curvature. It was noted when the ulcer had been located within the stomach that it still could not be detected by external palpation. This ulcer might have been missed by a blind gastrectomy. The patient was doing well six months following surgery.

CASE 5.—J. P., No. 476127, a 67-year-old Negro man, received 4,000 ml. of blood in a four-day period for massive gastrointestinal bleeding. He gave a history of epigastric pain of two weeks' duration. An x-ray examination with a barium meal was normal. Liver function studies were normal. At laparotomy inspection of the gastrointestinal tract showed no abnormality. A large gastrotomy revealed a 2.5 by 0.6 cm. shallow ulcer on the posterior wall of the stomach. A 70 per cent gastric resection was done. The patient developed an abdominal crisis forty-eight hours after operation, and an exploratory laparotomy was performed. He was found to have acute pancreatitis with extensive fat necrosis on the peritoneal surfaces. Cardiac arrest occurred immediately after operation. Cardiac function returned following a left thoracotomy and cardiac massage, but death occurred several hours later. Microscopic examination of the resected stomach demonstrated a large patent blood vessel in the base of the ulcer. An autopsy was not performed.

CASE 6.—D. H., No. 663344, a 77-year-old white woman, was admitted because of massive hematemesis and melena for twenty-four hours. She had not had any symptoms referable to the digestive tract. An x-ray examination with a barium meal showed no evidence of esophageal varices, but was unsatisfactory for evaluation of the stomach. A total of 3,000 ml. of blood was given in the first twenty-four hours in the hospital; a laparotomy was then performed. Palpation of the stomach and duodenum showed no abnormality. A gastrotomy was done and about 400 ml. of blood evacuated from the stomach. Two gastric ulcers, each about 1.5 cm. in diameter, were found in the mid-portion of the stomach near the lesser curvature. There was active bleeding from a blood vessel in the central portion of one of the ulcers. The ulcers were removed with a 70 per cent subtotal gastrectomy. The patient developed progressive cardiac failure twenty-four hours after surgery and expired forty-eight hours after surgery. No autopsy was obtained.

CASE 7.—E. B., No. 678959, was a 57-year-old white man with a five-month history of intermittent epigastric pain relieved by food. He was a known alcoholic. He was admitted to the hospital because of hematemesis, and received 1,000 ml. of whole blood. Liver function studies, repeated barium meals, and gastroscopy were negative. The patient did well on medical therapy until occult bleeding recurred at the end of the second hospital week. An exploratory laparotomy was then performed. Examination of the gastric mucosa through a large gastrotomy showed no abnormality. Because of the patient's typical peptic ulcer history, a "blind" 70 per cent gastric resection was performed. Examination of the resected specimen demonstrated a subacute ulcer of the gastric mucosa with marked inflammatory reaction in the submucosa. The patient was asymptomatic thirteen months after surgery. This was the only patient in the series in whom a lesion found in the resected specimen was not demonstrated by gastrotomy.

CASE 8.—C. F., No. 688273, a 48-year-old white man, was known to be a chronic alcoholic. He was admitted for a third episode of hematemesis in six months. X-ray studies with a barium meal two months before admission had shown no abnormalities. A total of 2,500 ml. of blood was given during the first eight hours after admission to the hospital. A Bromsulphalein test showed moderate impairment of liver function. An emergency x-ray examination with a barium meal showed a constant filling defect in the pyloric antrum that was strongly suggestive of a neoplasm. Surgical exploration was decided upon. At laparotomy the liver showed Laennec's cirrhosis of a moderate degree; this was confirmed by biopsy. There were a few large veins in the ligamentum teres; no other evidence of varices could be found. A large gastrotomy and duodenotomy failed to reveal a bleeding lesion. A blood clot found within the stomach presumably explained

the antral filling defect noted on barium meal. Portal venous pressure was 300 mm. of water. The abdomen was closed. The patient had no recurrence of bleeding five months after operation. The presumptive diagnosis is gastrointestinal bleeding due to undetected varices secondary to Laennec's cirrhosis.

CASE 9.—J. W., No. 685937, was a Negro man, 53 years of age. He was admitted for recurrent anemia over a period of three years; the hematocrit on admission was 10 per cent. Repeated x-ray studies with a barium meal and barium enema were negative. Free acid was present in the gastric secretions. A total of eight stool specimens were strongly positive for occult blood. At laparotomy palpation of the abdominal viscera showed no abnormalities. A gastrotomy showed an irregular, shallow, 5 by 2 cm. erosion on the lesser curvature in the mid-portion of the stomach that was slowly oozing blood. A smaller area adjacent to the erosion was scarred and probably represented a healed erosion. These areas were removed with a 70 per cent subtotal gastrectomy. The pathologic examination showed chronic gastritis and superficial erosions.

The patient was discharged from the hospital after an uneventful postoperative course. He returned four months after surgery with a severe anemia. There was occult blood in the stools, and the hematocrit was 8 per cent. X-ray studies of the intestinal tract were negative. There was no free acid or blood in the stomach. Multiple aspirations from a Cantor tube as it descended through the intestinal tract showed occult blood in the intestinal secretions for the first time in the upper jejunum. A laparotomy was decided upon. A gastrotomy was performed on the gastric remnant without detecting any abnormality. The mucosa of the small bowel from pylorus to ileocecal valve was directly visualized with a sigmoidoscope. This was done by making four separate enterotomies. No abnormalities could be found, so the abdomen was closed. A report from the patient's local physician seven months following surgery stated that the blood loss had persisted in the stools, and blood transfusions had been necessary. The cause of bleeding remains obscure, but may arise from superficial erosions in the gastric remnant.

CASE 10.—S. J., No. 689477, a 64-year-old Negro woman, was admitted for the treatment of anemia; the hematocrit was 15 per cent. The patient had had epigastric pain relieved by antacids for three years. There had been no episodes of gross bleeding from the digestive tract, but numerous stool specimens contained occult blood. Free acid was present in the gastric secretions. Several x-ray studies with a barium meal and barium enema showed no abnormalities. Renal function studies showed marked impairment of function. The serum nonprotein nitrogen averaged 57 mg. per cent on three determinations, the urinary specific gravity was uniformly 1.010, and the phenolsulfonphthalein urinary dye excretion was less than 10 per cent in two hours. An exploratory laparotomy was performed. No source of bleeding could be palpated. A large gastrotomy showed small erosions in the antrum and mid-portion of the stomach; all of the erosions were limited to the gastric mucosa. A 70 per cent gastrectomy was performed. Examination of the resected stomach in the pathology laboratory showed superficial mucosal erosions. These are shown in the resected stomach in Fig. 3.

A second laparotomy was performed twelve days after the gastrectomy because of intestinal obstruction and hemoperitoneum. A large hematoma in the mesentery of the transverse colon had eroded the wall of the colon and obstructed the lumen. No active bleeding point was found. The transverse colon was resected and an end-to-end anastomosis performed. Following the second operation, the patient continued to have occult blood in the stools, and renal failure developed with an elevation of the serum nonprotein nitrogen to 150 mg. per cent. The nonprotein nitrogen slowly decreased to 60 mg. per cent in the next few weeks, but the patient became psychotic and required continued

hospitalization. All stools continued to contain occult blood until death occurred five months after surgery. No autopsy was obtained. The persistent bleeding in this patient may have been secondary to renal failure.

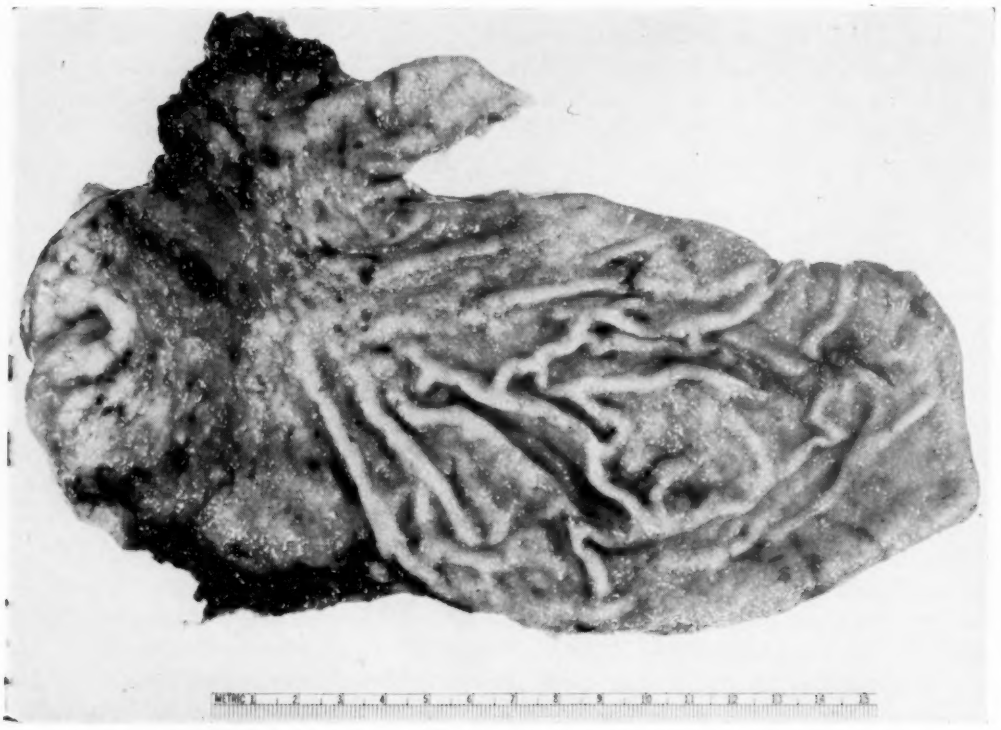

Fig. 3.—The resected stomach in Case 10. Multiple erosions are visible scattered throughout the gastric mucosa.

CASE 11.—O. G., No. 430691, a 52-year-old white woman, was admitted for repeated hematemeses after an excessive alcoholic intake of several days' duration. Two previous episodes of gastrointestinal bleeding had occurred during the preceding two years. X-ray studies of the stomach and duodenum had been negative.

She was operated upon as an emergency sixteen hours after admission after having received 3,500 ml. of blood. No lesion could be palpated in the stomach or duodenum. A gastrotomy revealed diffuse bleeding points in the gastric mucosa. An 85 per cent gastrectomy was done, but some bleeding continued from the gastric remnant. The spleen was removed and the gastrohepatic ligament divided up to the esophagus in order to devascularize the gastric remnant. The bleeding persisted; so the gastric remnant was packed with Gelfoam. The patient had received 8,000 ml. of blood during surgery, and her general condition at this time was too poor to tolerate a total gastrectomy. The bleeding stopped about five hours after surgery, but the patient remained comatose and died seven hours later. An autopsy showed superficial erosions in the gastric remnant.

DISCUSSION

The 11 patients reported here had no demonstrable cause for gastrointestinal bleeding on careful abdominal exploration. According to current concepts, they were candidates for blind gastrectomy. A wide gastrotomy, however, resulted in the demonstration of the bleeding lesion in 9 of these patients. In one patient (Case 7), a gastric erosion was missed on gastrotomy, removed by blind gastrectomy, and subsequently found by the surgical

pathologist. The other patient (Case 8) was a known alcoholic with cirrhosis of the liver who was operated upon because of x-ray findings which suggested a prepyloric carcinoma. Gastrotomy revealed that no lesion was present in the stomach; the bleeding was probably from esophageal varices. In Cases 1, 2, and 3 the bleeding lesions would likely have been missed by a 70 per cent blind gastrectomy because of their proximity to the cardia. In Cases 4, 5, and 6 the bleeding point would have been removed by a 70 per cent blind gastrectomy. Gastrotomy was of value in these patients, however, for a definite diagnosis was established, and extensive exploration of the small intestine was not necessary. In Case 2 a gastrectomy was avoided by the demonstration of a bleeding ulcer in a hiatus hernia.

In Cases 3, 9, 10, and 11 gastrotomy revealed multiple superficial bleeding points which were removed by subtotal gastric resection. The presence of mucosal erosions was demonstrated by microscopic examination in each instance. The frequency of superficial gastric erosions as the cause of undiagnosed gastrointestinal bleeding in this series is similar to that reported by others.[2, 3, 11, 13-15] Three of these 4 patients continued to bleed postoperatively. In Case 9, studies with a Cantor tube, four months after gastric resection, suggested bleeding in the upper small bowel, but no lesion could be found on surgical exploration. Cases 10 and 11 are considered to have had a diffuse bleeding diathesis due, respectively, to renal failure and alcoholic gastritis.

The value of gastrotomy in this series of cases is due to the extensive exposure obtained by the technique described. The dislike for gastrotomy expressed by many surgeons may be due to the unsatisfactory exposure obtained through a short gastric incision. It would seem unlikely that a superficial erosion hidden in a crevice between two folds of gastric mucosa could be found by any method that did not allow tension on the gastric mucosa in order to obliterate the mucosal folds.

Gastrotomy has also been criticized because of the time required and because of the soiling of the peritoneal cavity. Extension of the operating time is of little significance as compared to the dire consequences of missing a bleeding lesion in the gastric remnant. The 3 fatal cases cited by Gilchrist[4] and Cases 2 and 3 in this series are pertinent examples. Soiling of the peritoneal cavity is probably not an important consideration. The same degree of soiling occurs if the gastric remnant is inspected after a blind gastrectomy, as recommended by Cooper.[2] Failure to inspect the gastric remnant following blind gastrectomy carries the obvious hazard of missing the source of hemorrhage. There were no wound abscesses or peritoneal abscesses in the group of cases reported here.

The question arises as to the procedure to be followed when extensive examination of the gastric mucosa through a gastrotomy has been done and no lesion found. This problem was encountered in Case 7, and a blind gastrectomy was performed with a good result. It would seem that a gastrectomy is indicated in instances in which the upper gastrointestinal tract is almost surely the source of bleeding even though examination of the gastric mucosa through an adequate incision has not revealed the bleeding point.

SUMMARY

The operative management of 11 patients with gastrointestinal bleeding of obscure origin is described. When no abnormalities were found on palpation of the intestinal tract, the gastric mucosa was carefully inspected through a large gastrotomy opening. The source of bleeding was found in 9 patients. There were 4 patients with superficial gastric ulcers, 4 with multiple erosions, and 1 with an ulcer in a hiatus hernia. The patient with the hiatus hernia was treated by suture of the bleeding point and repair of the hiatus hernia. A subtotal gastrectomy was performed on the other patients. The bleeding area might well have been missed in some patients if it had not been visualized prior to gastrectomy. Three of the 4 patients with multiple erosions continued to bleed following subtotal gastrectomy; a total gastrectomy may have been the only operative procedure that would have cured these patients.

A gastrectomy was avoided in a patient with cirrhosis of the liver in whom a gastric neoplasm was suspected. Inspection of the interior of the stomach showed that a blood clot had caused the filling defect seen on a roentgenogram of the stomach.

The bleeding area was not found on examination of the gastric mucosa in 1 patient. A gastrectomy was performed, and a superficial erosion was found in the resected stomach.

The experiences with the 11 patients reported indicate that inspection of the gastric mucosa through a large gastrotomy is of much value in the operative management of patients with undiagnosed gastrointestinal bleeding.

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INTRAHEPATIC CHOLANGIOJEJUNOSTOMY IN A CASE OF BILIARY CIRRHOSIS WITH PORTAL HYPERTENSION

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THE technical problem of operations applied to the repair of cicatricial lesions of the common bile duct is considered one of the most difficult matters in all branches of surgery. In the majority of cases, these lesions result from an operative trauma during the course of operations in the right hypochondrium, especially cholecystectomies. Usually the accident is a direct consequence of a lack of familiarity, on the part of the surgeon, with the technical secrets of biliary surgery, or a result of difficulties inherent in the pathologic process which involves those structures.

The severity and extension of these lesions depend upon the nature and magnitude of the surgical trauma. The commonest accidents are incision, ligature, crushing, and excision. Despite the fact that they are serious injuries, on many occasions they are not recognized. There is no doubt, however, that effects from the overflowing of bile and pancreatic juice, usually infected, cause maceration, digestion, and fibrosis of the extrahepatic biliary ducts, which are added to the initial lesion. During complicated postoperative conditions we usually observe the formation of external or internal biliary fistula, and, later, the cicatrization that results in a more or less complete and extensive stenosis associated with jaundice.

In severe cases the destruction may involve the entire hepatocholedochus, after the destructive and cicatricial process extends to the hepatic hilum and the most protected portions of the retropancreatic segment of the common bile duct. Usually, when the destruction is not complete, one can mobilize the two segments and, after the resection of the narrowed portion, realize a mucosa-to-mucosa, end-to-end anastomosis followed by simultaneous drainage of the hepatocholedochus which a T tube inserted above or below the anastomosis. Even in cases in which the destruction involves a large portion of the hepatocholedochus, it is possible to find the retropancreatic segment of the duct and, by duodenal mobilization, advance it to the hepatic hilum in order to anastomose it to the proximal segment of the hepatic duct as suggested by Lahey[7] and Cattell.[2] Evidently these operations involve extreme technical difficulties, but if a stent drainage is maintained for more than six months in order to avoid the cicatricial retraction, the results are excellent since they preserve the sphincter of Oddi.

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Some surgeons prefer an end-to-side anastomosis between the proximal segment of the hepatocholedochus and the duodenum or jejunum, as advised by Walters, Waltman, and Cameron,[13] or an end-to-end Roux anastomosis with the jejunum, as advocated by Cole[3] and many others. If stent drainage is maintained for a considerable period of time, the results are good. The occasional bouts of cholangitis depend more on the biliary stenosis and obstruction than on the intestinal regurgitation. However, we prefer the Roux Y jejunal anastomosis in which reflux is less probable. We reserve, however, this type of biliary reconstruction for the cases in which end-to-end anastomosis is not possible between the two segments of the hepatocholedochus.

When the destruction involves all the hepatocholedochus, it is not possible to apply any of the anastomoses previously referred to, because there is no proximal stump and the cicatricial process involves the hepatic hilum, reducing it to a mass of fibrous tissue which continues with the intrahepatic fibrosis consequent to the biliary stasis (cirrhosis).

Under such circumstances the only solution is the intrahepatic biliary anastomosis. Unfortunately, attempts at biliary reconstruction have been completely unsuccessful through an anastomosis with a dilated duct that may be found in the liver surface. Also, the results of the intrahepatic duct anastomosis accomplished by a preliminary external biliary fistula, obtained by means of a transcutaneous puncture of the liver with the aid of a trocar, have not been successful. The detection of a large intrahepatic duct becomes imperative after the partial resection of a lobe of the liver, in view of the absolute failure of those efforts. This procedure, proposed and first accomplished by Longmire[9] in 1948, restores the biliary flow, anastomosing a large left lobe duct, partially resected, to a loop of the proximal jejunum (intrahepatic cholangiojejunostomy). Dogliotti[4] claims priority for this operation, stating that he performed it in 1946 when he anastomosed the stomach to an intrahepatic duct, which was discovered after partial resection of the left lobe of the liver (intrahepatic ductogastrostomy).

There is no doubt that the first publication regarding this subject must be credited to Longmire,[9] for it was after his initial work that new observations appeared. We must bear in mind that, besides the 6 instances of Dogliotti[4] in Italy, and that of Paschoud[12] in France, North American medicine is responsible for the furthering of literature pertaining to this work.

Lippman and Longmire,[8] in recent and careful review, found only 18 cases of intrahepatic cholangiojejunostomy to which they added 5 others, totaling 23 cases. Subsequently, Baron[1] published a personal observation that brings the number of cases already published to 24, without including the 6 of Dogliotti, in which the anastomosis was performed to the stomach (intrahepatic ductogastrostomy).

This technique has been uniformly indicated in cases in which no other method of reconstruction of the hepatocholedochus was possible. In 6 patients, the operation was performed for palliative purposes; these were patients with malignant obstruction. In the other cases, the indications for operation resulted from benign cicatricial stenosis consequent to operative trauma.

The aim of this work is to present a case of intrahepatic cholangiojejunostomy for postoperative cicatricial stenosis which we believe is deserving of comment.

CASE REPORT

D. B., a 27-year-old Brazilian half-caste married woman, was admitted to Hospital dos Servidores do Estado (Hospital for the Government Employees) on Sept. 13, 1954. In December, 1952, she had undergone a cholecystectomy at the Central Penitentiary Hospital (Federal District). A drain left in the common bile duct did not function and was immediately withdrawn. Following this, bile oozed through the opening for one month, when finally the fistula healed. Approximately one week later, she had severe attacks of colic and jaundice associated with light-colored stools and dark urine. From then on, the jaundice persisted and the attacks of colic were repeated with some frequency. In April, 1954, she was reoperated upon in the twenty-third Ward of the House of Mercy (Federal District) without success. Her symptoms, particularly the jaundice, were greatly aggravated after a transcutaneous intrahepatic cholangiography performed at that same clinic fifteen days after the previous intervention. The yellow-greenish skin color was changed to a dark pigmentation. Her condition became worse, rapidly and progressively.

Physical examination revealed a normally developed patient of average build, very weak and thin (34 Kg.), febrile (37.2° C.), and with melanic jaundice, and bilateral ocular xanthelasma. The abdomen was slightly curved and tense, and painful due to the scar of the earlier right supraumbilical transrectal laparotomy. Hepatomegaly was present about two inches below the costal margin. The other systems did not present abnormalities of enough interest to note. The laboratory examinations revealed marked anemia, with hyperbilirubinemia (indirect: 9.5 mg. per cent), while the hepatic function tests showed that the liver was involved (3 plus).

With the diagnosis of hepatocholedochus cicatricial stenosis, after one month of careful preparation she was operated upon again (biliary exploration by the right paramedian transrectal laparotomy) on Sept. 13, 1954. The incision through the abdominal wall and the access to the hilus were extremely difficult because of the dense adhesions, and more particularly due to the difficulties of hemostasis resulting from the extensive collateral circulation which, at the level of the peritoneum, seemed almost angiomatous. During the detachment of the duodenum, which was strongly adherent to the liver inferior face, there was duodenal fraying, and we observed bile-colored fluid in its interior that caused suspicion about the possible existence of biliary fistula, but it was absolutely impossible to identify any holes in the inferior face of the liver. Retrograde catheterization through the papilla was not possible, because of the destruction of the distal segment of the choledochus. Despite the fibrous mass of a bony consistency to which the hilus was reduced, we managed to identify the elements of the hepatic pedicle, but the remains of the hepatocholedochus were not found. Several aspirations at the level of the hilus were made, with the aim of reaching an intraglandular duct. These were negative, and it was perceived that the fibrosis in the liver was also solid. As it was impossible to find a solution to the case, and in view of the precarious condition of the patient, the abdomen was closed, and a subhepatic Penrose drain was left.

The immediate postoperative conditions were relatively uneventful, except on the tenth and eleventh days, when hematemesis appeared in a moderate degree. On Nov. 9, 1954, a transcutaneous liver aspiration was performed in the epigastric region whereby it was possible to puncture a large intrahepatic duct. A polyethylene tube (No. 190) was passed through the trocar and subsequently replaced by one of greater caliber (No. 240). During the first days of the drainage, 600 c.c. of bile was obtained daily; this amount progressively decreased until it became nil at the end of approximately one month. The attempts to re-establish the drainage were unfruitful. The patient's general condition, however, had improved considerably although she continued to have melanic jaundice, acholic stools, and febrile bouts of cholangitis.

On March 14, 1955, an intrahepatic cholangiojejunostomy was performed after the resection of nearly half of the left lobe of the liver (Fig. 1). The anastomosis of the intrahepatic duct with the jejunum was of the end-to-end precolic type, the suture of mucosa to mucosa being possible without difficulty. We re-established the continuity of the intestines using Roux Y principle, while the jejunal loop, near the anastomosis, was attached to the hepatic section (Fig. 2). The ducts' permeability and the communication between the two lobes had been determined previously by means of biliary explorations and

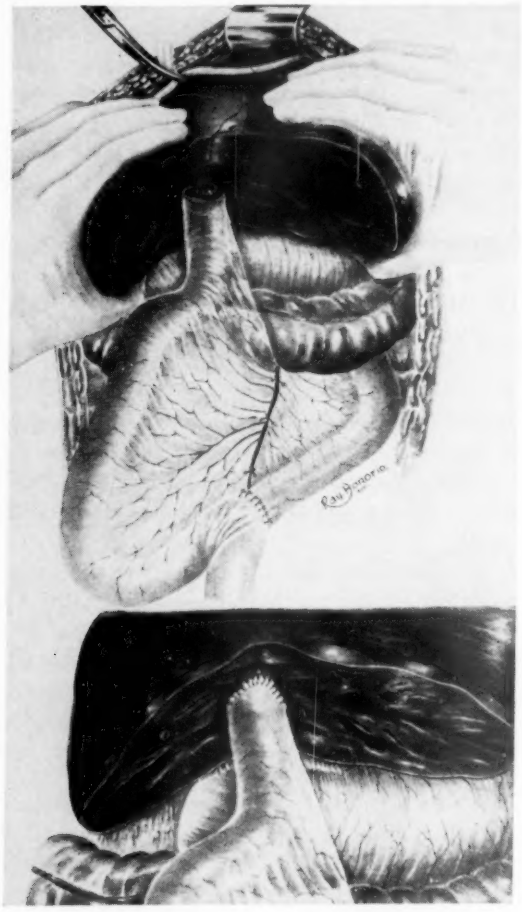
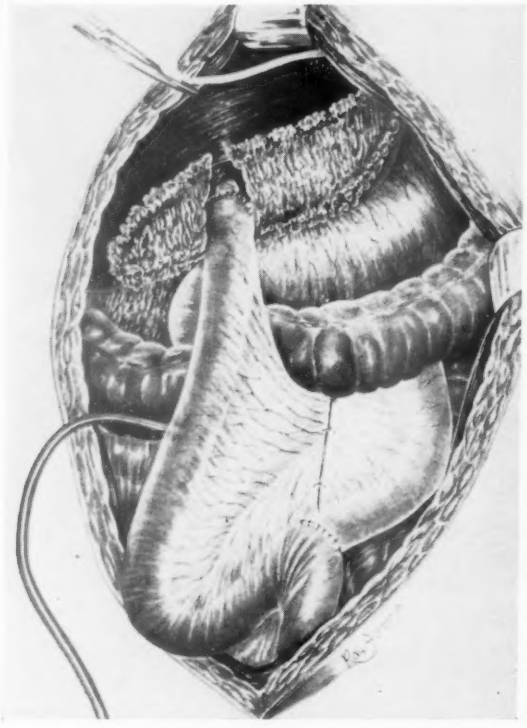


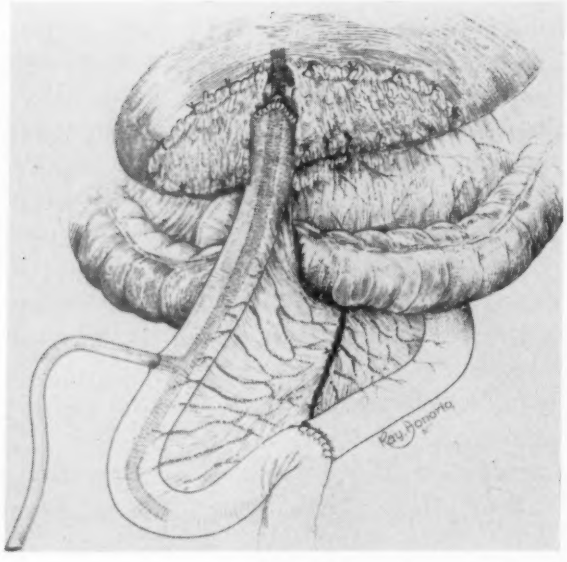
Fig. 1.—The beginning of the end-to-end anastomosis of the intrahepatic duct to the proximal jejunal loop is seen above. The manual compression aids the hemostasis previously made by U-shaped points.

by operative cholangiography (Fig. 3). A Kerr tube with long branches was located at the level of the anastomosis, which passed through the jejunum and out by the left transrectal stab wound. Penrose's drains were located in the left subphrenic region. The immediate response was eventful, becoming complicated by prolonged abdominal distention and evident signs of aggravation of the hepatic involvement. The biliary drainage through the Kerr tube was about 200 c.c. daily. On the third day the patient had severe hematemesis, which came under control immediately. On the fifth day colored feces were evacuated spontaneously. After the tenth day there was an abundant drainage of purulent biliary secretion, with fever and an aggravation of the general condition. Soon after, clinical and radiological signs of left subphrenic collection occurred, with atelectasis of the pulmonary basis on this same side, which responded to the specific antibiotic medication after a short period.

One month after the operation, the patient was well and was evacuating dark feces and urine of practically normal color. However, the liver function tests were unsatisfactory. There was still purulent biliary secretion that cleared up some days later. The patient's condition progressively improved. She regained her vivacity and appetite, lost her yellowish color, and put on weight. The hepatic function tests at the same time confirmed the above improve-



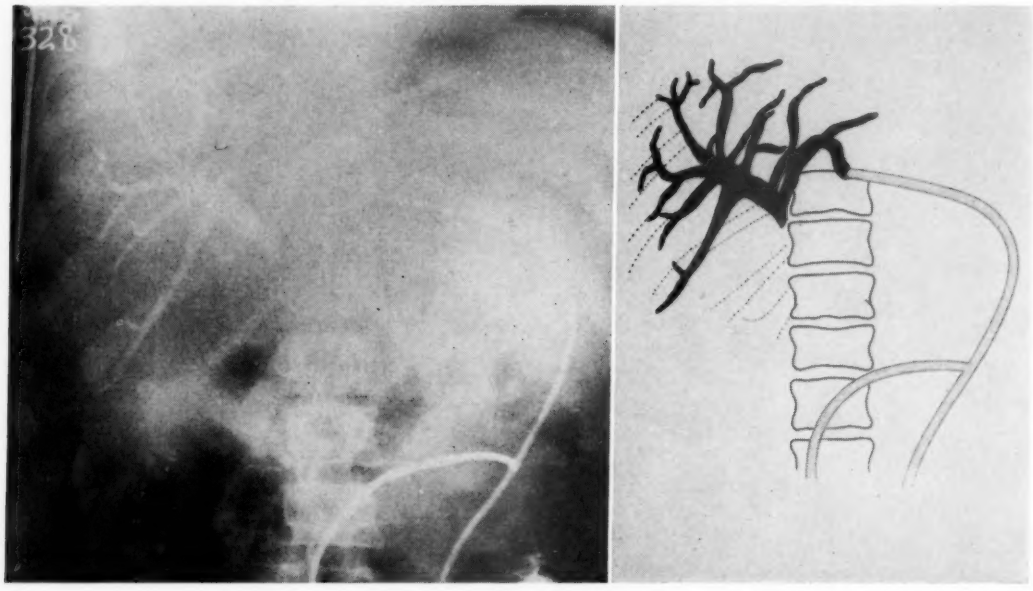
A.



B.

Fig. 2.—Finished cholangiojejunostomy, a Kerr's tube of long branches being maintained through the suture region, as observed in the schematic reproduction. A Y-shaped jejunostomy and eppiploplasty of the hepatic section region were performed.

ments. The Kerr drain was withdrawn after six months, when drainage was already being interfered with by the accumulation of mudlike bile. When she was last examined in October, her general condition was good. The abdomen was soft; she was without pain and had gained 5 Kg. in weight. Her stools and urine were normal; however, some jaundice continued. The hepatic tests showed that the liver was still moderately affected.



A. *B.*

Fig. 3.—Preoperative cholangiography obtained through the Kerr's tube after the anastomosis is finished. Observe that the fibrosis reaches the proximities of the interlobar communication.

COMMENT

Without a doubt the intrahepatic cholangiojejunostomy constitutes one of the most brilliant acquisitions of modern surgical technique. Its indication, however, must be reserved to special cases of extreme destruction, when the more physiologic reconstructive operations are impracticable. It is true that these extremely difficult operations are excessively tiring, and therefore they require the detection of the hepatocholedochus in a cicatricial core. Usually, this detection is very difficult, due to the intense fibrosis and to the disappearance of the regions of repair and to the normal loss of anatomic relations. Furthermore, the fact cannot be ignored that when the attempts at cicatricial repair are repeated, the difficulties increase with the detection of the extrahepatic duct and therefore decrease the possibilities of surgical success.[7] However, the mere presumption of difficulties does not justify the use of intrahepatic cholangiojejunostomy, which must be reserved for cases where the proximal stump of the common hepatic is impossible to detect.

Contrary to our opinion, Baron[1] judges this operation to be easier and of minor character, and he stresses that it must precede, in severe cases, any attempt at reconstruction of the extrahepatic biliary ducts. In the first place, we are not in accordance because, although the intrahepatic cholangiojejunostomy eliminates the hard work of dissection of the pedicle fibrous mass, we cannot consider it an easy operation. On the contrary, in our opinion, it is an opera-

tion of major character, with many technical requirements and numerous obstacles. In the second place we disagree because the intrahepatic anastomosis, in spite of partially sacrificing one lobe of the liver, is executed with a duct greatly reduced in caliber from the common hepatic duct, and, therefore, biliary overflow is more difficult and cicatricial stenosis more probable. By studies of the observations published up to the present, we note that although the intervention has resolved a desperate situation, which executed in another manner would prove insoluble in many cases, the results of intrahepatic anastomosis are inferior to those of the usual reconstructive operations of the hepatocholedochus. Surely the experience and accomplishment of the technique will improve these results, but we believe that its indication will persist as an exception to those instances without other surgical possibility. However, with excessive zeal we should not indefinitely defer a legitimate indication, allowing the biliary cirrhosis to progress to a point of strangulating the hepatic parenchyma and making it severely insufficient. Our case demonstrates this. The long period during which the patient persisted in complete biliary obstruction (twenty-seven months) certainly is responsible for the difficulties and the relative deficiency of the result. If the degree of the biliary cirrhosis had not been so advanced, the result certainly would have been better. This procedure must be used relatively early so that the results of the intervention will not be nullified by the advanced and irreversible hepatic lesion. In our case, we must emphasize the fact that the cirrhosis was aggravated after the execution of the transcutaneous intrahepatic cholangiography which was performed in another clinic. Indefinite retention of the injected contrast considerably aggravated the patient's condition, and by all appearances, it contraindicated its use in similar conditions. However, the intrahepatic cholangiography may be of great usefulness when reserved for the surgical intervention, and used shortly before the liver resection, when we are positive of the immediate elimination of the contrast. Practiced in this way, it may result in the detection of a large left biliary duct, necessary for the anastomosis, in addition to determining whether the fibrosis does or does not interrupt the biliary communication between the two lobes of the liver. The former would make the prognosis much worse because of the necessity of a bilateral anastomosis and the danger of greater sacrifice of parenchyma in the resection of each lobe.[11] Fortunately, the blocking of the communication between the two lobes by fibrosis appears to be an exceptional occurrence, as Lippman and Longmire observed.[8] Furthermore, there is the possibility of the establishment of a communication between the two great lobes through the liver caudate segment.

Another point in our case which is worthy of mention is the presence of portal hypertension, evidenced by repeated and fulminating hematemesis, as well as profuse collateral circulation found during the surgical intervention, and splenomegaly. The histologic sections showed that there was intense fibrous proliferation, compressing the hepatic parenchyma and more particularly the portal vein branches and the biliary ducts in the portal space (Figs. 4 and 5). The abdominal musculature looked like a bloody sponge, while the parietal

peritoneum and the epiploons presented an angiomatous aspect as the number of vessels was excessive. As a consequence of the above, the hemostasis was

Fig. 4.

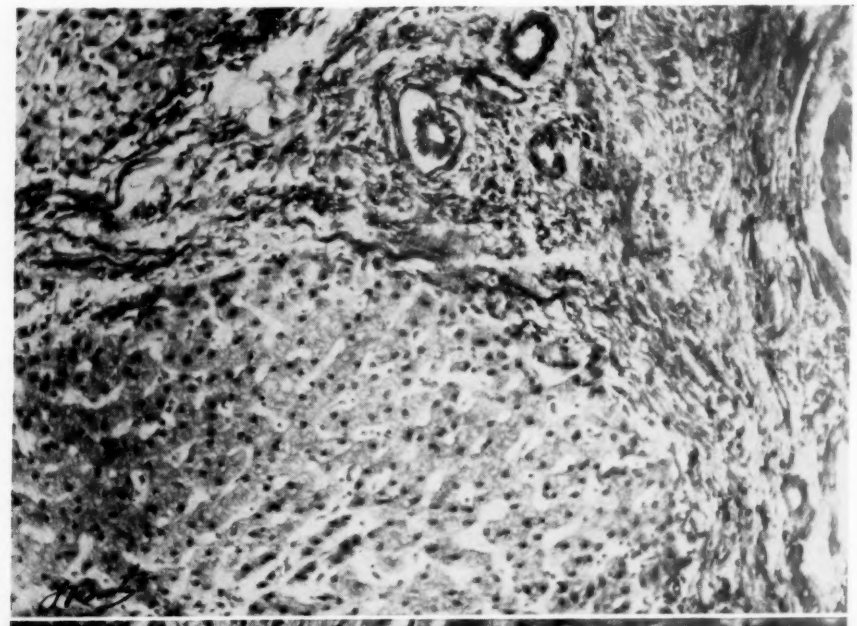


Fig. 5.

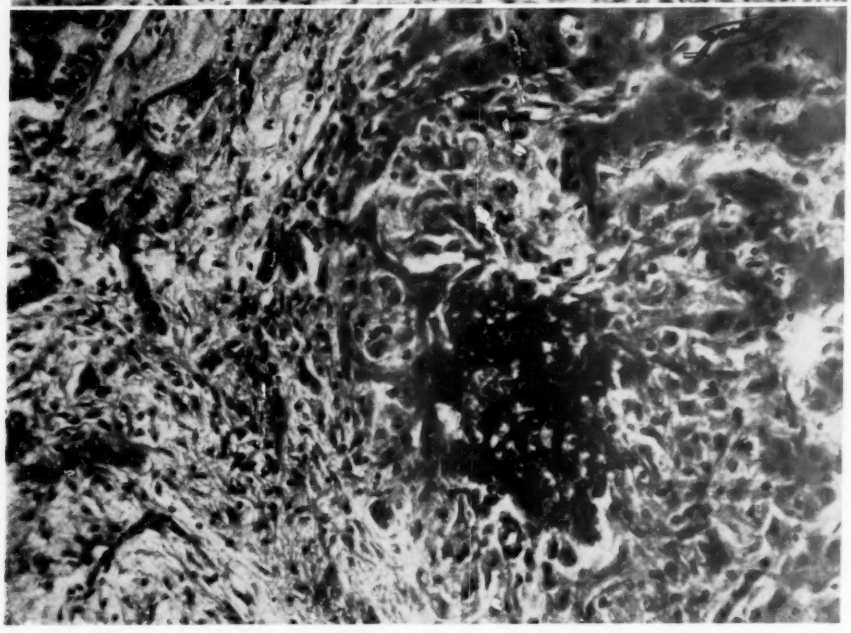


Fig. 4.—Connective proliferation at the level of the portal space. Conserved lobular architecture (hematoxylin and eosin).

Fig. 5—"Biliary lake" in the peripheral portion of the hepatic lobe. In the perilobar connective and portal tissue there is a discrete tendency to canalicular proliferation.

so difficult that sometimes it seemed uncontrollable, rendering the exposure difficult and delayed (two hours).

The occurrence of portal hypertension in the case of biliary cirrhosis is considered exceptional. It was not found in a series of 30 cases studied by MacMahon and Mallory.[10] Gibson and Robertson[6] also only mentioned it in two cases of 240 observed. Ellis and Holman,[5] recently, based on a personal observation, insisted upon the rarity of this occurrence. Above all, we believe that this incidence is not so uncommon, especially in advanced cases such as ours. We must bear in mind that in most of the published observations of cases in which an intrahepatic cholangiojejunostomy was practiced, there were evident signs of portal hypertension. This is evident, for example, in the five last cases reported by Lippman and Longmire,[8] in which portal hypertension was present in three. Portal hypertension, therefore, does not appear to be a condition of the rarest type, particularly in the advanced cases when its presence greatly increases the difficulty of intervention and aggravates the prognosis.

SUMMARY

We have reported a case of choledochus cicatricial stenosis (postcholecystectomy), the correction of which had been attempted on three previous occasions, and proved unfruitful, due to the complete destruction of the hepatocholedochus. The partial resection of the left lobe of the liver was performed with a Roux Y end-to-end anastomosis of a large intrahepatic duct with the jejunum (intrahepatic cholangiojejunostomy). The case is particularly interesting not only because of the type of anastomosis used, but also because of the gravity of the biliary cirrhosis which was associated with portal hypertension. Although we stress our point of view that this intervention must be reserved for the extreme cases in which a more natural solution is not possible, we are, however, of the opinion that improved results may be obtained with this procedure when applied at an early stage.

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CARCINOID TUMORS OF THE DUODENUM

A Review of the Literature and a Report of Two Cases

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PRIMARY tumors of the duodenum are rare, and carcinoid tumors are among the least common found in this location. Ebert[3] reviewed 23 primary tumors of the duodendum, 3 of which were carcinoids. However, Hoffman and Grayzel[7] found no cases of carcinoid in 18 tumors of the duodenum, and Raiford[14] reported only one case of carcinoid in a series of 21 duodenal tumors.

Of the combined 62 duodenal tumors reported by the above authors, 27 (45 per cent) were malignant and 35 (55 per cent) were benign. Carcinomas were by far the most common malignant lesions, and adenomas the most common of the benign tumors. Myomas, pancreatic rests, lipomas, and hemangiomas were next most common among the benign tumors in this order. The least common benign tumors were cystic tumors, fibroadenomas, lymphangiomas, and carcinoids.

In a review of the literature, we are able to find a total of 26 cases of carcinoid tumors of the duodenum (Table I). Twelve of these cases were symptomatic and the remainder were found incidentally. In most of the symptomatic cases, there was a history of vomiting, upper abdominal pain, or jaundice. None had gastrointestinal bleeding. We are adding to the literature two cases of carcinoid tumor of the duodenum, in one of which there were repeated episodes of severe gastrointestinal hemorrhage.

CASE REPORTS

Case 1.—The patient, a 60-year-old white male farmer, was first admitted to the medical service of this hospital on Jan. 1, 1955, with a history of vague gnawing, griping epigastric and right lower quadrant pain, associated with generalized abdominal soreness, of three months' duration. This symptom complex was poorly described and bore no relation to food, was not present at night, and was not rhythmic. Eight days prior to admission the patient had tarry stools which persisted, and eventually symptoms of weakness and dizziness occurred. Physical examination at this time was unremarkable except for obesity and slight epigastric tenderness. There were hard black feces in the rectum. The erythrocyte count was 2,170,000; hemoglobin 6.0 Gm.; and hematocrit 19 per cent. Gastric analysis revealed free hydrochloric acid, and an upper gastrointestinal x-ray series and barium enema showed no abnormalities other than a diverticulum of the second portion of the duodenum. The patient was transfused with 1,000 c.c. of whole blood on the night of admission and placed on a bleeding-ulcer regimen. No further bleeding occurred during this hospitalization, and he was discharged on Feb. 2, 1955, with a normal blood count, and instructed to follow an ulcer diet.

On Feb. 22, 1955, he was readmitted to the medical service because of homologous serum hepatitis, with symptoms of two weeks' duration. He was treated with a high protein, high carbohydrate diet and bed rest, resulting in symptomatic improvement and return of liver function tests toward normal. While in the hospital on this occasion, he

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began to have tarry stools and a fall of hemoglobin and erythrocyte count. He complained intermittently of vague right upper quadrant and mid-epigastric tenderness. Repeat gastrointestinal roentgen studies revealed no additional findings. He was transfused with 1,000 c.c. of whole blood, and after the blood count stabilized and liver function tests became normal, he was discharged on May 19, 1955.

He was recalled to the medical service on July 21, 1955, for re-evaluation. History revealed that he had continued to have vague abdominal discomfort. There had been no recurrence of gastrointestinal bleeding. Complete studies again failed to reveal any pertinent positive findings other than the diverticulum, which was not thought to be the source of his bleeding. He was therefore transferred to the surgical service for exploratory laparotomy.

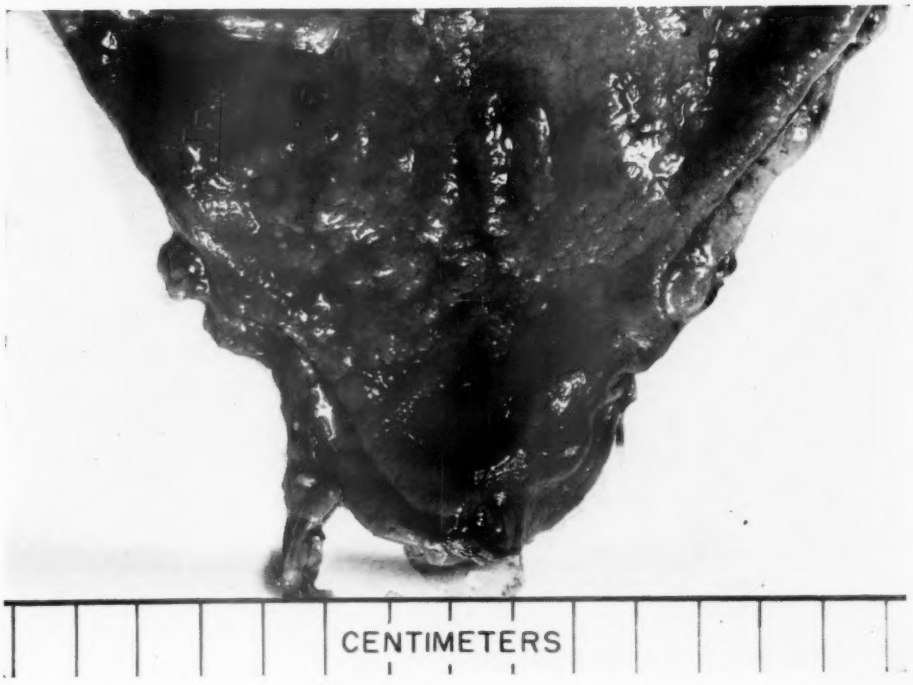

Fig. 1.—Case 1. Note sessile prominence just beyond pyloric ring. Note also the central depression suggesting previous ulceration.

Operation: Laparotomy was performed on Aug. 17, 1955. Adhesions were found in the right lower quadrant secondary to an old appendectomy. The small bowel was thoroughly examined and no lesions found. The liver was small, but otherwise normal, and the gall bladder was unremarkable. Some induration was noted in the head of the pancreas, and the possibilities of a duodenal ulcer or infection in the duodenal diverticulum were considered. Therefore, subtotal gastric resection was performed. Upon transection of the duodenum, a mass about the size of a large pea was seen just distal to the pylorus. The tumor was located in the submucosa and was of a firm consistency. Close inspection of the overlying mucosa revealed depression, redness, and thinning, suggesting that there had been recent ulceration, but there was no active ulceration at this time. The duodenal diverticulum showed no abnormality.

Pathological examination: Gross examination of the resected portion of the stomach and duodenum showed a normal-appearing gastric mucosa. Just distal to the pylorus there was a submucosal mass measuring 1.6 by 1.0 cm. (Fig. 1). The mucosa overlying the tumor was quite thin, but there was no evidence of ulceration. The cut surface of the tumor was yellow and firm. Microscopic examination revealed a small tumor lying within the submucosa of the duodenum (Fig. 2). The tumor was composed of nests of

TABLE I. SUMMARY OF REPORTED CASES OF CARCINOID OF THE DUODENUM

YEAR REPORTED	AUTHOR	LOCATION	SIZE	AGE	SEX	SYMPTOMS	METASTASIS	RESULT
1929	Wolfer	First portion, anterior duodenum	0.6 cm.	49	M	Peri-umbilical pain, belching, vomiting	None	Surgically removed. No follow-up
1931	Cooke	Duodenum, upper portion				None	Not given	Not given
1931	Cooke	Duodenum, upper portion				None	Not given	Not given
1932	Raiford	Anterior wall, proximal duodenum		49	M	None	None	Surgically removed. Follow-up unknown
1934	Feyrter			58	M	None	None	
1934	Feyrter			40	M	None	None	
1934	Feyrter			58	M	None	None	
1934	Feyrter			88	M	None	None	
1939	Brunschwig	Infrapapillary duodenum and ampulla of Vater		41	F	Pancreatic insufficiency due to obstruction of main pancreatic duct	None	Minimal symptoms of pancreatic insufficiency after 15 months' follow-up
1939	Porter and Whelan	Duodenum		64	F	None	None	Incidental finding at autopsy
1944	Ritchie and Stafford	Duodenum		56	F	None	None	
1949	Pearson and Fitzgerald	Duodenum				None	None	
1949	Pearson and Fitzgerald	Duodenum, first portion	1.0 cm.			None	None	
1951	Warren and Coyle	Duodenum and ampulla of Vater		46	M	Indigestion, 5 years; obstructive jaundice, 3 mo.		Surgically removed. Developed destructive rib lesions and died 4 years later. No autopsy

1951	Hannan	Duodenum, first portion	1.2 × 1.5 × 1.8 cm.	64	M	Upper abdominal pain	None	Surgically removed. Well 2 years later
1951	Hannan	Duodenum, first portion	1.6 × 1.4 × 0.9 cm.	63	M	Dyspepsia and jaundice	None	Surgically removed. Well 4 months later
1951	Hannan	Duodenum, first portion	3 × 2 × 2 cm.	70	F	Epigastric pain	None	Surgically removed. Well 3 years later
1952	Foreman	Duodenum	0.6 cm.	42	F	Epigastric pain, vomiting, diarrhea	None	Not given
1953	Ebert	Duodenum	Two nodules each 0.6 cm.	64	F	None	None	Incidental finding
1953	Ebert	Duodenum, first portion	1.0 × 1.0 cm.	63	M	None	None	Incidental finding
1953	Ebert	Duodenum, first portion	0.3 cm.	60	M	None	None	Incidental finding
1953	Mrazek	Duodenum, anterosuperior portion	1.2 × 0.6 cm.	62	M	High partial gastrointestinal obstruction	None	Surgically removed. Well 21 months later
1953	Mrazek	Duodenum and ampulla of Vater	Not given	61	M	Nausea, vomiting, diarrhea, jaundice	Spread to pancreas	Surgically removed. Died with recurrent tumor and jaundice
1953	Mrazek	Duodenum, first portion	0.5 cm.	57	M	Weakness and weight loss	Extensive to liver and lymph nodes	Death due to liver metastases
1954	O'Sullivan and Bowe	Duodenum		63	M	Epigastric pain and vomiting	None	Surgically removed. Also had chronic duodenal ulcer. Asymptomatic at 6 months' follow-up
1955	Ilgenfritz and Mathews	Duodenum, second portion	3.5 × 3.0 cm.	49	F	Known liver tumor for 14 years. Liver biopsy showed carcinoid 6 years prior to death	Massive to liver, regional lymph nodes	Death due to cardiac failure
1955	Barnes and Young	Duodenum, first portion	1.0 × 1.6 cm.	62	M	Repeated episodes gastrointestinal hemorrhage	None	
1955	Barnes and Young	Duodenum, first portion	Two tumors, 0.5 cm. each	56	M	None		Incidental finding at autopsy

Fig. 2.

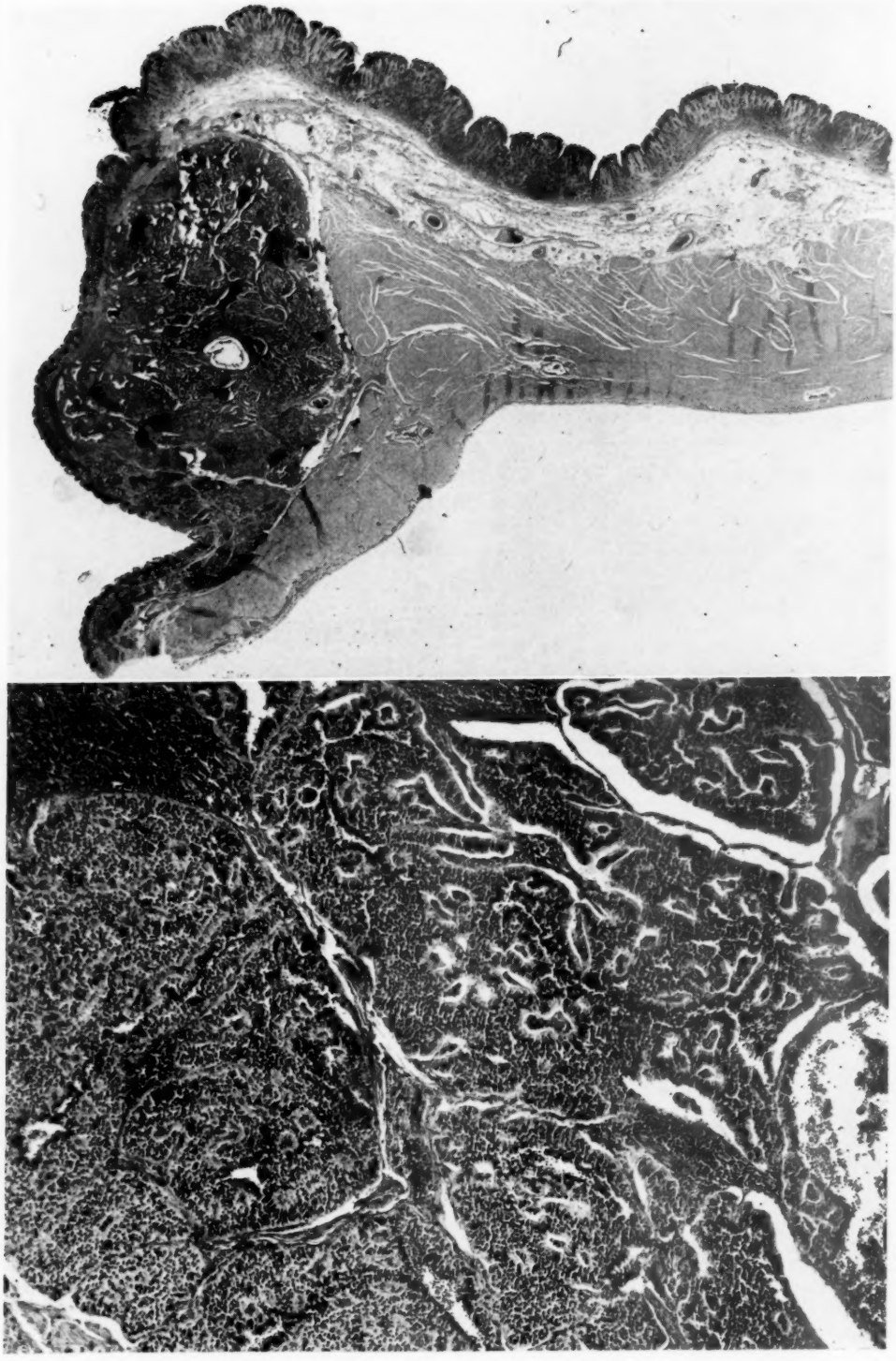

Fig. 3.

Fig. 2.—Case 1. Longitudinal section through entire lesion to reveal thin overlying mucosa and vascularity of tumor.

Fig. 3.—Case 1. High-power magnification to show typical cell nests and pseudoalveolar arrangement. Hematoxylin and eosin (×60; reduced ⅕).

small cells which were regular in size and shape and contained small, ovoid basophilic nuclei of uniform size (Fig. 3). No mitoses were noted. The histologic appearance was typical of a carcinoid tumor. There was no evidence of lymphatic invasion or extension

Fig. 4.

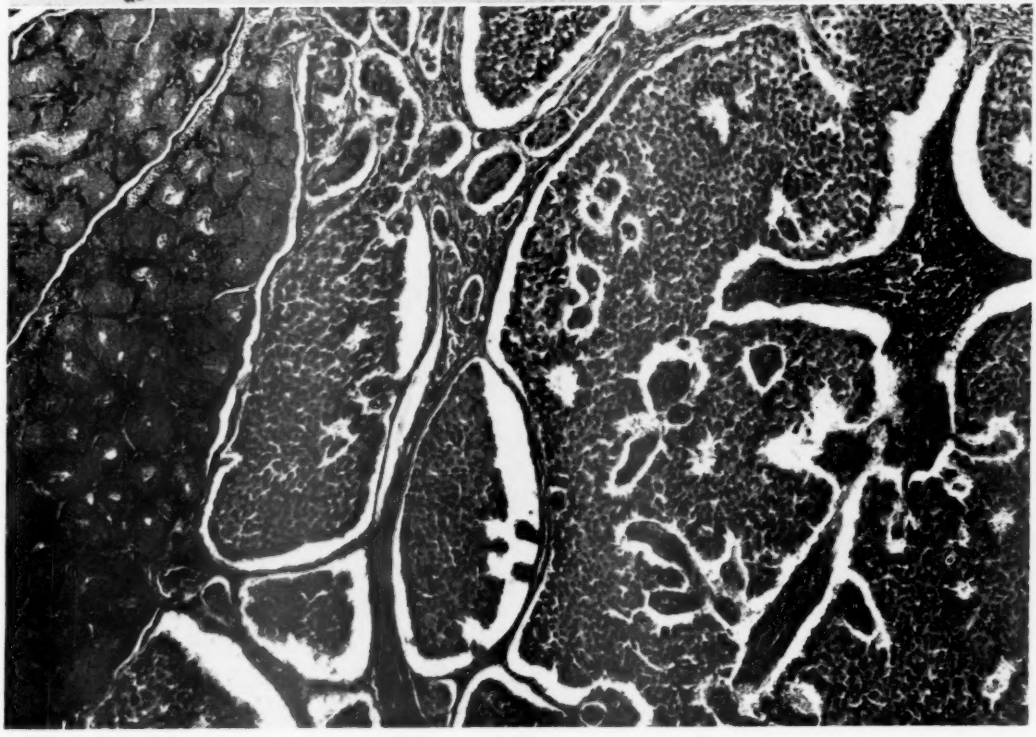

Fig. 5.

Fig. 4.—Case 2. Low-power magnification of larger of the two duodenal carcinoids showing superficial location and pattern.

Fig. 5.—Case 2. High-power magnification of smaller lesion to reveal typical carcinoid structure. Hematoxylin and eosin (×60; reduced ⅕).

of the tumor into the muscularis. Numerous vascular channels coursed through the tumor. The overlying mucosa was very thin and revealed cellular fibrosis beneath it, indicating previous ulceration.

CASE 2.—The patient, a 56-year-old Negro man, was admitted to this hospital on July 27, 1950, with the diagnosis of squamous cell carcinoma involving the right paranasal sinuses, origin undetermined, but possibly from the nasopharynx. He was given x-ray therapy, but became progressively worse and died on Dec. 22, 1950. An autopsy revealed carcinoma of the nasopharynx with involvement of the right maxillary and sphenoid sinuses, lobular pneumonia of both lower lobes, focal encephalomalacia, and two small carcinoid tumors of the first portion of the duodenum, each measuring 0.5 cm. in diameter (Figs. 4 and 5). A review of his history revealed that these lesions had been asymptomatic and there was no evidence of metastasis.

DISCUSSION

Tumors of the duodenum produce symptoms of upper abdominal pain, nausea, vomiting, diarrhea, and hemorrhage.[14] Frequently the picture is that of high upper gastrointestinal obstruction. If the tumor involves the ampulla of Vater, jaundice occurs. These symptoms are characteristc of both benign and malignant lesions. If the tumor is malignant and there are metastases, other constitutional symptoms appear. The physical findings usually consist of epigastric or right upper quadrant tenderness, distention, and, if hemorrhage has occurred, anemia. Roentgenologic study may show a filling defect in the duodenum.

An analysis of 12 symptomatic cases of carcinoid of the duodenum (Table I) shows that the predominant symptoms include upper abdominal pain, nausea, vomiting, jaundice, and diarrhea. In the 3 cases with jaundice, carcinoid involving the ampulla of Vater was found. In one case there were signs of marked pancreatic insufficiency due to obstruction of the main pancreatic duct at the ampulla of Vater. Two cases with massive liver metastases presented no gastrointestinal symptoms related to the primary lesion. One of these had weakness and weight loss, and death was due to the liver metastases. In the other case there was evidence of a liver tumor of 14 years' duration, and liver biopsy 6 years prior to death showed carcinoid. The patient died of cardiac failure unrelated to the carcinoid.

The diagnosis of the type of duodenal tumor can be made only by surgical exploration and pathologic study of the lesion. Hannan, Hazard, and Wise[6] reported 3 cases of carcinoid of the duodenum with x-ray evidence of a rounded filling defect in the first portion of the duodenum. They stated that the radiologic findings were not specific for carcinoid. The gross appearance of a carcinoid tumor of the duodenum seen at operation is usually that of a firm, fairly well-demarcated, submucosal tumor which may vary in size from 0.3 to 3.5 cm. in diameter. The cut surface of the tumor is usually yellow. Hannan and associates[6] suggested that the absence of mucosal ulceration overlying the lesion may be helpful in differentiating this tumor from a true carcinoma, and that frozen section may be of value.

Of the 12 symptomatic cases, 10 patients underwent surgical exploration with excision of the tumor. Although the reported follow-up in each case is of short duration, there was no evidence of recurrence or metastases in 6 of 10 cases. No follow-up was given in 2 cases. In one case with involvement of the ampulla of Vater and obstructive jaundice there was a recurrence of the

tumor, with jaundice, and the patient died. Autopsy revealed carcinoid with spread to the pancreas, but there were no distant metastases. A second patient with obstructive jaundice died 4 years after surgical removal of the tumor. Prior to death there was evidence of destructive rib lesions. Autopsy was not performed.

It is evident that carcinoid tumors of the duodenum may metastasize, although the patient may live for many years with metastases. Adequate excision of the primary tumor and removal of all the metastatic lesions possible would seem to give a hope of cure and of long-term palliation.

All evidence in our case with symptoms of gastrointestinal bleeding points to the carcinoid as the source of hemorrhage. Although hemorrhage due to carcinoid tumors is unusual, it can occur. Martin and Atkins,[9] in a review of the literature of carcinoid tumors of the stomach, found that in 3 cases there was gastrointestinal bleeding. In our case, there was no evidence that the duodenal diverticulum had ever been involved by an inflammatory process, and surgical exploration revealed no other possible source of hemorrhage. Although there was no active ulceration of the mucosa overlying the lesion at the time of operation, the mucosa was quite thin with scarring underneath, and it is very likely that the bleeding was from this site.

SUMMARY

Two cases of carcinoid tumor of the duodenum are reported. One patient was symptomatic and had suffered repeated episodes of gastrointestinal bleeding, an unusual occurrence from such a tumor. The related literature is reviewed.

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A CLINICAL STUDY OF 51 CASES OF MESENTERIC INFARCTION

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INTRODUCTION

EVEN though the mortality of intestinal obstruction has sharply decreased since the turn of the century, the mortality of mesenteric vascular occlusion has not. It is still about 80%. In the world's literature there are reports of only relatively few recoveries. Though Elliot[10] reported the first successful resection for mesenteric infarction as long ago as 1895, Uricchio,[29] in 1954, was able to collect only 158 cases in which recovery followed bowel resection. These sobering facts stimulated our review of the 51 cases of mesenteric infarction seen at the University of Minnesota Hospitals between Jan. 1, 1942, and April 1, 1954. We hoped that this study might clarify some of the factors responsible for the high mortality of this abdominal catastrophe. All cases of mesenteric vascular occlusion admitted during this period were included except those where the occlusion was secondary to mechanical intestinal obstructions. The diagnosis was made by postoperative pathologic or postmortem examination in 47 cases, while in the other 4 instances definite operative findings were used to make the diagnosis even though the pathologic appearance of the resected specimen was not conclusive.

ETIOLOGY

Vascular occlusion in this disease can be either arterial or venous. In our series of cases (Table I) arterial occlusion occurred more than twice as often as venous occlusion, but this difference may not be general. In large collective

TABLE I. TYPES OF MESENTERIC VASCULAR OCCLUSION

I. Arterial		29
A. Superior mesenteric artery thrombosis	13	
B. Superior mesenteric artery embolus	10	
C. Superior and inferior mesenteric artery thrombosis	3	
D. Superior mesenteric and celiac arterial thrombosis	1	
E. Periarteritis nodosa	1	
F. Superior mesenteric artery cut and repaired at surgery	1	
II. Venous		12
A. Superior mesenteric vein thrombosis	9	
B. Portal vein thrombosis	1	
C. Inferior and superior mesenteric venous thrombosis	1	
D. Superior mesenteric veins cut and repaired at surgery	1	
III. Unknown*		10
Total		51

*The clinical picture in these cases suggest they were mainly instances of arterial occlusion in which the thrombus or embolus was dislodged at post-mortem examination.

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reviews, the incidence has been about equal (Bowen[3]). There was little difference in the frequency of arterial thrombosis as compared to arterial embolism.

Primary mesenteric arterial occlusion is usually due to arteriosclerotic or rheumatic cardiovascular disease (Table II). It is also caused occasionally by subacute bacterial endocarditis, periarteritis nodosa, and blood dyscrasias. There was a clinical diagnosis of cardiovascular disease in 80 per cent of the cases of mesenteric arterial occlusion in our series. It is interesting to note, however, that generalized arteriosclerotic changes in the mesenteric arteries are unusual even when marked arteriosclerosis is present in the aorta, coronary, and renal vessels. As a rule, only 1 to 2 cm. at the origin of the superior mesenteric artery is minimally involved (Carucci[5]).

TABLE II. DISEASES ASSOCIATED WITH MESENTERIC VASCULAR OCCLUSION

I. Cardiovascular Disease		33
A. Arteriosclerotic or hypertensive heart disease without failure	25	
B. Congestive heart failure	6	
C. Subacute bacterial endocarditis	1	
D. Periarteritis nodosa	1	
II. Recent Abdominal Surgery		10
A. Abdominal visceral cancer	5	
B. Splenectomy for blood dyscrasia	1	
C. Miscellaneous	4	
III. Infections		2
A. Recent appendicitis	1	
B. Thrombophlebitis of cecum	1	
IV. Blood Dyscrasias		2
A. Polycythemia vera	1	
B. Hemolytic jaundice (congenital)	1	
V. Miscellaneous		4
A. Pancreatitis	1	
B. Carcinoma of pancreas	1	
C. Diabetes mellitus	2	
Total		51

Recent abdominal surgery was the second most frequent condition associated with mesenteric infarction in our series. We found laparatomy had been performed within thirty days preceding admission in 19.5 per cent (10 cases). Others have reported this association in 30 to 40 per cent of the cases (Laufman,[15] Seybold[24]). Perhaps the most frequently reported operation preceding mesenteric infarction is splenectomy for congenital hemolytic jaundice. However, in our series, this was the case in only one patient, whereas 50 per cent had undergone a recent extensive abdominal cancer operation.

The cause of mesenteric venous thrombosis is frequently obscure. Berry[1] and Johnson[12] have emphasized this point. No inciting factor was evident in half (55.5 per cent) of our cases. However, in the few cases in which the cause seemed clear, peritonitis, blood dyscrasias, and operative trauma were responsible.

CLINICAL PICTURE

Pathologically one can differentiate between arterial occlusion due to an embolus, or thrombus, and venous thrombosis, but clinically this distinction is not possible. There are, however, two general types of the disease clinically. In

one there is a sudden, complete occlusion of a major mesenteric artery, while in the other there is a gradual occlusion of the artery or vein. When massive intestinal infarction is reached, the clinical picture is about the same no matter how it started.

TABLE III. COMPARISON OF SIGNIFICANT CLINICAL FACTORS IN SUPERIOR MESENTERIC VENOUS AND ARTERIAL OCCLUSION

	Arterial occlusion (35 cases)	Venous occlusion (9 cases)
A. Physical Findings		
Vomiting	63.9%	100%
Abdominal distention	39.3%	100%
Shock	26.2%	11.1%
Fever	35.9%	11.1%
B. Other Factors		
Mortality	88.6%	11.1%
Surgical mortality	66.7%	NONE
Associated cardiovascular disease	73.8%	22.2%
Presence of both large and small bowel infarction	30.3%	11.1%

Sudden occlusion of a major artery usually occurs in a patient with a history of cardiac disease. We found that when cardiac decompensation was present it did not change the picture of this abdominal disease but it frequently overruled the possibility of mesenteric infarction in the mind of the attending physician until the patient was nearly moribund. The onset of this abdominal catastrophe is characterized by sudden, severe, cramplike abdominal pain which is unrelenting and may radiate into the back. There frequently is a great disparity between the severity of the abdominal pain and the physical findings of the abdomen. Nausea and vomiting soon appear and shock follows. Hematemesis

and melena are uncommon. Though abdominal distention is minimal, signs of peristalsis soon disappear. Abdominal and rebound tenderness frequently precede a moribund state by only a few hours. Fever over 100° F. (orally) is infrequent. Leukocytosis with neutrophilia is the rule.

All patients do not have this rapid fulminating clinical progression. In fact, the disease progresses quite slowly in some. In our series over one-half of the patients with mesenteric venous or arterial thrombosis and one-third of those with arterial embolus had symptoms one week or more before seeking medical care. When there is gradual occlusion, three stages may be noted. First, there is a vague prodromal period characterized by intermittent abdominal pain which is usually colicky in nature. This pain may occasionally be precipitated by meals, and accompanied by mild nausea and perhaps vomiting. Bowel irregularity may occur. Abdominal distention is mild, and the passage of flatus does not give the relief usually expected. This stage may be present for days. Second, there is a period of intestinal paresis and minimal distention, which is followed by the third stage of intestinal infarction with all its consequences. Once infarction is present, abdominal pain is persistent, abdominal rebound and tenderness become definite, and shock follows within hours.

There is no laboratory test pathognomonic of mesenteric infarction. Nevertheless, leukocytosis and neutrophilia are nearly always present (see Table IV). Melena is significant, and should be tested for by a stool guaiac or a diagnostic saline enema when infarction is suspected. A serum amylase test should be done to rule out acute pancreatitis.

TABLE IV. SIGNS AND SYMPTOMS OF MESENTERIC VASCULAR OCCLUSIONS PRESENT ON HOSPITAL ADMISSION (PERCENTAGE)

Abdominal pain	100.0
Abdominal tenderness	90.0
Neutrophilia over 80 per cent	91.0
Leukocytosis over 13,000 per cubic millimeter	88.8
Abdominal rebound	81.3
Decreased or absent bowel sounds	72.7
Vomiting	71.2
Pulse over 100 per minute	66.7
Abdominal distention	51.2
Auricular fibrillation	39.2
Fever over 100° F. (oral)	31.2
Melena	30.0
Shock	23.5
Hematemesis	13.3
Abdominal mass	5.9

A diagnostic peritoneal aspiration is also useful. Sanguineous ascitic fluid is invariably present in mesenteric venous thrombosis (Berry and Bougas,[1] Rabinovitch[23]). It was noted in 78 per cent of our cases. However, bloody ascites is less frequent in mesenteric arterial occlusion. During the past year we have been able to detect small amounts of bloody ascitic fluid when ordinary methods failed, by inserting a polyethylene tube with multiple perforations. It is introduced through a No. 13 trocar aspiration needle and directed toward the pelvis from a point just below the umbilicus while the patient is in a high Fowler's position.

The x-ray findings in mesenteric infarction were not pathognomonic. There was usually mild to moderate gaseous distention of the stomach, small and large bowel, with or without fluid levels—a picture suggesting ileus. It was unusual to see signs of mechanical obstruction. A few patients did, however, have moderate distention of small and large bowel which stopped at the transverse colon or splenic flexure. Harrington[11] considers this finding, when coupled with a barium enema showing no mechanical obstruction, strongly suggestive of mesenteric vascular occlusion. The extreme absence of intestinal gas suggesting fluid-filled loops was an infrequent but important finding. In our experience this picture in an acutely ill patient is evidence of strangulating obstruction. Another interesting finding in one patient was pneumatosis cystoides intestinalis.

MORTALITY AND TREATMENT

In a recent review of cases of bowel obstruction at the University of Minnesota Hospital, mesenteric infarction carried the highest mortality—76.5 per cent. Although it occurred in only 3.6 per cent of all cases of bowel obstruction, mesenteric infarction comprised 34.3 per cent of the cases with gangrenous bowel obstruction. The incidence of this catastrophe comprised a greater proportion of gangrenous bowel obstructions than others have reported (Bollinger,[2] McIver,[18]). The reason for this high incidence compared to other series is not apparent.

TABLE V. MORTALITY DATA

	DEATHS	PER CENT MORTALITY
I. Patients with nonsurgical treatment (28 cases)		
A. Death due to massive infarction	27	
B. Necrotizing hemorrhagic pancreatitis	1	
Total Deaths	28	100
II. Patients with surgical exploration (3 cases)		
A. No resection		
1. Cardiac arrest during anesthetic induction	1	
2. Unrecognized infarction	1	
3. Exploration without resection	1	
Total Deaths	3	100
B. Resection and primary anastomosis (20 cases)		
1. Peritonitis due to leak in anastomosis	2	
2. Marked extension of infarction	2	
3. Associated gangrene of both legs	1	
4. Shock and sepsis of massive infarction	1	
5. Hypertensive encephalopathy	1	
6. Periarteritis complicated by cardiac failure and pulmonary edema	1	
Total Deaths	8	40

A careful analysis of our data suggests the mortality of mesenteric infarction depends primarily upon delay in diagnosis, the type of occlusion, i.e., arterial or venous, and the length of infarcted bowel. There were nine patients not moribund on admission who did not have the correct diagnosis made clinically or by exploratory laparotomy during the first twenty-four hours after hospital admission. Our mortality would have been lower if a diagnostic

peritoneal aspiration had been done and exploratory laparotomy had been performed in those patients having bloody ascites and/or the findings of abdominal tenderness with a leukocytosis over 13,000 white blood cells per cubic millimeter.

The difference between the mortality of venous and arterial occlusion was striking. Only 1 of 9 patients (11.1 per cent) having superior mesenteric venous thrombosis died, and there was *no operative death,* even though massive resections (over 200 cm. of bowel) were performed in three patients. On the other hand 88.6 per cent (31 of 35) of the cases with superior mesenteric arterial occlusion succumbed. However, where only a small resection (less than 200 cm. bowel) was necessary, the mortality was only 11.1 per cent regardless of the etiology. Consequently we believe the high mortality of arterial occlusion is probably due to its sudden onset, more massive nature, and frequent occurrence in patients with pre-existing cardiovascular disease (Table III).

Aggressive surgery is the most adequate treatment for mesenteric infarction. Large resections of the small bowel may be compatible with life, especially if the terminal ileum is preserved. There were patients in this series who survived after resection of all but 2½ feet of small bowel. Twelve of twenty patients having primary resection and anastomosis survived operation. An additional two patients survived operation and later died of unrelated causes. Excluding these two cases the mortality rate among patients with bowel resection was 30 per cent.

Whether postoperative anticoagulant therapy will improve surgical treatmen of mesenteric infarction has not been clearly established. In our series there was no statistical difference in mortality when adequate anticoagulant therapy was given. However, it was interesting to note the following: (1) There was no extension of thrombus at post-mortem examination in any case which received adequate postoperative anticoagulant therapy; (2) At post-mortem examination, there was extension of superior mesenteric artery thrombosis following massive resection in 3 of 4 patients who received no postoperative anticoagulants.

Even though there was no difference in mortality where postoperative anticoagulant therapy was given, these observations suggest that anticoagulants are useful in preventing further propagation of a thrombus following adequate resection of infarcted segments of bowel.

Supportive antibacterial chemotherapy is indicated in mesenteric vascular occlusion. Experimentally life is prolonged when these drugs are given by retarding bacterial proliferation and probably delaying penetration into the gut when its viability is impaired. From our study no definite conclusions can be drawn as to their efficacy because a control group of patients was not available.

DISCUSSION

Mesenteric vascular occlusion remains a challenge in the treatment of bowel obstruction today. With the increase of longevity and cardiovascular disease, this abdominal catastrophe will play a greater role in the future. How can this problem be met?

Perhaps the greatest decrease in mortality of this disease can be made by earlier diagnosis. Unexplained abdominal pain, tenderness, and leukocytosis especially in a patient with cardiovascular disease is good evidence of mesenteric infarction. It is important to remember that the onset of this disease is not always sudden, severe, and rapidly fulminating. The presence of bloody ascites or melena is confirmatory evidence of infarction, but one should not delay exploratory laparotomy awaiting these findings. The mortality of a negative celiotomy is negligible, but laparatomy with adequate bowel resection early in the course of mesenteric infarction is lifesaving.

A vital question in the surgical treatment of mesenteric infarction is how much bowel is necessary to sustain life. At the turn of the century many patients with mesenteric thrombosis were operated upon without resection because life was not thought possible if only a few feet of small bowel remained. Ample evidence now exists to show that two-thirds of the small bowel can be resected without severe consequences, and there are many reports of patients surviving 90 per cent resection of the small bowel. We are now following a 28-year-old man in our clinic who, some months after having a subtotal gastrectomy for peptic ulcer, suffered a volvulus of the small bowel necessitating resection of all but one foot of intestine from the ligament of Treitz to the cecum. His weight has stabilized, and he is now returning to work. There is little doubt that many patients with mesenteric infarction can be saved through aggressive surgery.

SUMMARY AND CONCLUSIONS

1. A report of 51 new cases of mesenteric infarction has been presented.

2. Cardiovascular disease and recent abdominal surgery were the conditions most frequently associated with mesenteric vascular occlusion.

3. There were no pathognomonic signs in mesenteric infarction, but abdominal pain and tenderness, decreased bowel sounds, and leukocytosis with neutrophilia in the presence of a normal serum amylase were characteristic findings.

4. Superior mesenteric venous and arterial occlusion presented similar clinical pictures, but had much different prognoses.

5. The over-all mortality of superior mesenteric arterial occlusion was 88.6 per cent as compared to 11.1 per cent for mesenteric venous occlusion. Reasons for this difference are discussed.

6. The mortality of mesenteric infarction can only be reduced by the more frequent judicious use of diagnostic laparatomy in elderly patients having unexplained abdominal pain.

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BLOOD VOLUME CHANGES IN THE AGED

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THIS study of the blood volumes of 92 men and women 70 years and older was undertaken to define the limits of blood volume in geriatric patients. Relatively small changes in the direction of deficit or excess in this elderly group may be poorly tolerated, and the interpretation of a single blood volume determination is often made difficult through lack of appropriate standards for comparison. Published data relating to the thesis that there are significant changes in blood volume occurring with advancing years are relatively rare and inconclusive. Gibson and Evans[9] in 1937 suggested that blood volume tends to decline with age, but of their subjects, only 3 of the group of 90 were over the age of 60 years. Cohn and Shock[6] have reported that studies in 60 men over the age of 50 years revealed no significant changes in blood or plasma volume per unit of body weight. No comparable studies have been made in older women. Therefore, this survey of the blood volumes in the geriatric patient seemed justifiable.

The subjects were ambulatory, active, and apparently healthy men and women on the geriatric custodial wards of a state hospital. Weight changes were used to help assess the nutritional stability of the subjects, and a change greater than plus 10 or minus 5 pounds during the preceding year excluded that individual from the study. All subjects were fasting, and the blood volume determinations were made in the early part of the day. The Evans blue dye T-1824 was used to measure the serum volume according to the method of Gregerson,[10] which involves a single sample of blood withdrawn ten minutes after injection of the dye. In addition, serum proteins,[15] hemoglobin,[8] hematocrit, and, in some instances, serum sodium,[12] potassium,[12] chloride,[11] and gamma globulin[16] were determined. Hematocrit values were corrected by factors of 0.96[4] for trapped plasma, and 0.91[5] for difference in venous and body hematocrit. In selected individuals, the blood volume determination was repeated at one- to two-month intervals with satisfactory agreement. Thirty-six men and 56 women with mean ages of 76.2 and 77.1 years, respectively, were investigated. There were 26 men and 38 women in the 70- to 80-year-old group, 8 men and 17 women in the 80- to 90-year-old group. Two men and one woman were over 90 years. In respect to height, the entire group appeared below average; in respect to weight, they were well nourished. Hemoglobin, hematocrit, and serum protein values were well within normal range.

RESULTS

Table I summarizes blood volume data of 36 men, 70 to 94 years of age, in terms of total blood volume, red cell volume, and serum volume in milliliters,

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TABLE I. BLOOD VOLUME IN AGED MEN

PATIENT	AGE (YR.)	HT. (CM.)	WT. (KG.)	S.A. ($M.^2$)	HCT. (VOL. %)	HGB. (GM. %)	PROT. (GM. %)	BLOOD VOLUME (ML.)	BLOOD VOLUME (ML./KG.)	RBC VOLUME (ML.)	RBC VOLUME (ML./KG.)	SERUM VOLUME (ML.)	SERUM VOLUME (ML./KG.)	SERUM VOLUME (ML./$M.^2$)
G. S.	70	163.2	64.1	1.68	48.5	16.5	7.32	5,320	83.0	2,354	36.7	2,965	46.3	1,770
J. P.	70	167.6	80.5	1.88	49.2	17.4	7.00	4,899	60.9	2,190	27.2	2,709	33.7	1,440
G. K.	70	177.8	73.2	1.89	44.6	16.7	6.69	5,654	77.2	2,290	31.3	3,364	46.0	1,780
Y. S.	70	157.5	50.0	1.47	42.7	16.0	6.74	4,033	80.7	1,567	31.3	2,466	49.3	1,680
H. H.	71	170.8	67.7	1.78	39.3	15.4	6.17	5,725	84.6	2,247	33.2	3,478	51.4	1,950
X. S.	71	166.4	75.5	1.83	48.9	17.2	6.63	4,970	65.8	2,216	29.4	2,754	36.5	1,510
R. S.	71	167.6	60.0	1.66	39.1	14.1	6.59	3,757	62.6	1,334	22.2	2,423	40.4	1,460
C. T.	71	147.3	60.4	1.52	45.1	15.6	5.79	4,050	67.1	1,701	28.2	2,349	38.9	1,550
M. Z.	71	157.5	47.4	1.44	45.0	15.9	6.00	3,585	75.6	1,466	30.9	2,119	44.7	1,470
S. E.	72	160.0	90.0	1.93	48.4	17.9	6.79	5,934	65.9	2,720	30.2	3,214	34.7	1,670
G. N.	72	166.4	66.4	1.73	39.4	14.3	5.79	3,590	54.1	1,287	19.4	2,303	35.2	1,330
R. P.	72	161.3	69.2	1.72	43.9	15.6	5.75	4,158	60.1	1,659	24.0	2,499	36.1	1,450
R. H.	72	180.4	55.5	1.70	40.4	13.5	6.33	4,544	81.9	1,762	31.7	2,782	50.1	1,640
P. T.	72	165.1	86.0	1.92	44.9	16.3	5.73	5,157	60.0	2,106	24.6	3,051	35.5	1,590
J. C.	72	161.3	59.1	1.61	34.1	11.9	6.18	5,240	88.7	1,563	26.4	3,677	62.2	2,280
J. Z.	74	153.0	64.1	1.60	36.6	14.9	7.74	4,797	74.8	1,756	27.4	3,041	47.4	1,900
E. V.	74	167.6	60.9	1.68	46.5	16.4	6.64	4,449	73.1	1,882	30.9	2,567	42.2	1,530
K. F.	74	172.7	58.7	1.67	44.3	14.8	6.49	4,504	76.7	1,813	30.9	2,691	45.8	1,610
T. V.	75	169.5	73.6	1.83	43.6	15.6	6.78	6,029	81.9	2,390	32.5	3,639	49.4	1,990
J. K.	75	175.3	60.0	1.71	45.0	15.6	6.58	4,931	82.2	2,017	33.6	2,914	48.6	1,700
C. P.	75	161.3	66.4	1.70	41.4	15.1	6.87	4,093	61.6	1,543	23.2	2,550	38.4	1,500
J. N.	75	167.6	72.7	1.81	47.6	16.1	6.46	5,551	76.4	2,420	33.3	3,131	43.1	1,730
F. S.	76	165.1	58.2	1.62	42.8	15.7	6.18	4,938	84.8	1,926	33.1	3,012	51.8	1,860
W. S.	77	170.2	75.9	1.86	49.4	16.7	6.70	5,385	70.9	2,417	31.8	2,968	39.1	1,600
P. V.	77	160.0	64.6	1.66	43.3	15.4	6.87	3,833	59.3	1,510	23.4	2,323	36.0	1,400
W. L.	77	167.6	58.3	1.63	43.1	14.5	6.90	3,927	67.4	1,540	26.4	2,387	40.9	1,460
J. M.	80	154.9	44.1	1.38	42.5	15.3	6.55	3,697	83.8	1,429	32.4	2,268	51.4	1,640
L. M.	80	152.4	57.3	1.52	48.6	17.1	6.10	3,110	54.3	1,378	24.0	1,732	30.2	1,140
A. L.	81	163.2	60.9	1.64	42.9	16.6	6.74	4,099	67.3	1,787	29.3	2,312	38.0	1,410
L. M.	82	166.4	64.1	1.71	45.5	16.0	7.43	4,900	76.4	1,981	30.9	2,919	45.5	1,710
S. S.	82	160.0	80.4	1.83	45.3	16.2	6.13	4,299	53.5	1,771	22 0	2,528	31.4	1,380
J. F.	84	162.6	60.5	1.63	45.0	15.2	6.74	3.677	60.8	1,504	24 9	2,173	35.9	1,330
I. V.	85	165.1	52.7	1.56	40.6	13.9	7.00	4,086	77.5	1,508	28.6	2,578	48.9	1,650
J. D.	89	170.2	72.7	1.83	47.1	16.9	6.79	4,826	66.4	2,065	28 4	2,761	38.0	1,510
A. H.	91	161.3	55.9	1.57	37.3	13 4	7.33	4,496	80.4	1,541	27.6	2,955	52.9	1,880
G. G.	94	161.9	58.6	1.61	43.9	14.1	8.15	4,137	70.6	1,655	28.2	2,482	42.4	1,540
Mean	76	164.4	64.6	1.69	43.8	15.6	6 63	4,566	71.3	1.842	28 5	2,725	42 7	1,610

TABLE II. BLOOD VOLUME IN AGED WOMEN

PATIENT	AGE (YR.)	HT. (CM.)	WT. (KG.)	S.A. ($M.^2$)	HCT. (VOL.%)	HGB. (GM. %)	PROT. (GM. %)	BLOOD VOLUME (ML.)	BLOOD VOLUME (ML./KG.)	RBC VOLUME (ML.)	RBC VOLUME (ML./KG.)	SERUM VOLUME (ML.)	SERUM VOLUME (ML./KG.)	SERUM VOLUME ML./$M.^2$
L. D.	70	157.4	40.8	1.35	42.5	15.3	6.95	3,240	79.4	1,252	30.7	1,988	48.7	1,470
A. S.	70	127.0	37.7	1.12	39.4	13.9	5.68	3,232	85.7	1,157	30.7	2,075	55.0	1,850
G. M.	70	162.6	47.7	1.43	44.0	15.0	6.74	3,574	74.9	1,432	30.0	2,142	44.9	1,500
L. R.	70	157.5	70.5	1.71	37.7	13.7	5.60	4,575	64.9	1,569	22.3	3,006	42.6	1,760
M. P.	70	152.4	63.7	1.59	40.5	13.6	6.36	3,511	55.1	1,292	20.3	2,219	34.8	1,400
P. D.	70	160.0	64.6	1.66	34.6	12.2	6.06	3,207	49.6	1,012	15.6	2,195	34.0	1,320
A. P.	70	162.6	63.3	1.66	45.7	15.0	5.84	2,677	42.3	1,114	17.6	1,563	24.7	940
A. S.	71	160.0	73.2	1.75	42.5	15.4	7.26	3,236	44.2	1,251	17.1	1,985	27.1	1,130
I. D.	71	163.8	74.1	1.80	42.2	14.8	6.85	5,120	69.1	1,966	26.5	3,154	42.6	1,750
A. D.	72	156.2	53.2	1.51	42.7	16.1	6.95	2,838	53.3	1,212	22.7	1,626	30.6	1,080
M. B.	72	158.8	42.7	1.39	40.9	15.0	6.70	2,926	68.5	1,088	25.5	1,838	43.0	1,320
E. C.	72	157.5	50.9	1.49	35.3	12.4	5.53	4,712	92.6	1,512	29.7	3,200	62.9	2,150
Z. Z.	73	153.0	42.7	1.35	36.7	15.3	7.16	3,438	80.5	1,264	29.6	2,174	50.9	1,610
M. S.	73	154.3	65.5	1.63	40.5	14.6	7.49	3,050	46.6	1,123	17.2	1,927	29.4	1,180
E. B.	74	157.5	65.5	1.65	37.3	13.1	5.93	4,950	75.6	1,695	25.9	3,255	49.7	1,970
M. H.	74	160.0	48.6	1.47	39.0	13.7	6.18	2,872	59.1	1,022	20.8	1,859	38.3	1,260
E. P.	74	163.8	56.4	1.59	42.4	15.1	6.13	5,074	90.0	2,065	36.6	3,009	53.4	1,890
A. H.	74	157.5	56.4	1.55	40.4	13.6	6.80	3,333	59.1	1,225	21.7	2,108	37.4	1,360
E. L.	75	163.8	74.1	1.80	39.5	13.4	6.33	4,445	60.0	1,586	21.4	2,859	38.6	1,590
E. S.	75	147.3	43.6	1.32	39.8	14.0	6.36	3,256	74.7	1,179	27.1	2,077	47.6	1,570
M. T.	75	157.5	73.2	1.73	35.8	13.5	6.64	3,730	51.0	1,343	18.4	2,387	32.6	1,380
I. N.	75	147.3	53.2	1.44	36.5	13.7	6.08	3,105	58.4	1,029	19.4	2,076	39.0	1,440
S. H.	75	121.9	45.5	1.19	38.6	14.2	7.74	2,636	57.9	924	20.3	1,712	37.6	1,440
J. G.	75	138.4	78.2	1.63	47.5	16.7	6.58	4,931	63.1	2,133	27.3	2,798	35.8	1,720
E. D.	75	149.9	57.3	1.51	44.8	15.4	6.23	3,667	64.0	1,494	26.1	2,173	37.9	1,440
A. B.	76	152.4	40.5	1.31	39.2	14.2	6.50	2,656	65.6	947	23.4	1,709	42.2	1,300
A. N.	76	160.0	51.0	1.50	42.0	14.1	6.36	3,618	70.9	1,382	27.1	2,236	43.8	1,490
F. M.	77	147.3	57.8	1.49	37.7	14.8	6.33	3,880	67.1	1,464	25.3	2,416	41.8	1,620
L. H.	77	165.1	80.0	1.86	37.4	14.0	6.64	5,060	63.3	1,897	23.8	3,163	39.5	1,700
H. D.	77	157.5	43.2	1.38	39.0	13.6	6.55	3,569	82.6	1,265	29.3	2,304	53.3	1,670
O. K.	77	152.4	52.3	1.46	36.9	13.3	5.97	3,469	66.3	1,164	22.2	2,305	44.1	1,580
M. M.	78	151.1	46.4	1.39	39.4	13.9	6.55	2,996	64.6	1,073	23.2	1,923	41.4	1,380
L. L.	78	154.9	49.1	1.45	40.0	15.6	7.10	2,952	60.1	1,181	24.0	1,771	36.1	1,220
M. T.	78	153.7	61.8	1.59	42.2	14.9	5.97	3,614	58.5	1,390	22.5	2,224	36.0	1,400

L. S.	78	156.2	53.7	1.51	41.3	13.8	5.73	3,006	56.0	930	17.3	2,076	38.7	1,370
M. R.	78	146.1	69.1	1.60	42.1	15.2	5.84	3,721	53.8	1,425	20.6	2,296	33.2	1,440
B. C.	79	149.9	47.8	1.40	41.9	14.6	6.22	3,480	72.8	1,323	27.7	2,157	45.1	1,540
P. C.	79	162.6	50.9	1.52	41.8	14.9	6.60	2,738	53.8	1,042	20.5	1,696	33.3	1,120
C. C.	80	151.1	42.7	1.33	38.0	13.5	6.13	3,296	77.2	1,137	26.6	2,159	50.6	1,620
E. O.	80	157.5	60.9	1.60	43.3	15.4	6.69	3,761	61.8	1,484	24.4	2,277	37.4	1,420
E. S.	80	142.2	60.5	1.48	45.3	16.0	6.22	4,533	74.9	1,870	30.9	2,663	44.0	1,800
L. S.	80	170.2	54.6	1.61	39.8	14.6	6.22	3,960	72.5	1,433	26.2	2,527	46.3	1,570
E. M.	80	154.9	61.4	1.59	43.5	14.9	6.90	4,000	65.1	1,581	25.7	2,419	39.4	1,520
A. S.	81	146.1	41.8	1.29	38.8	15.0	6.27	2,450	58.6	951	22.7	1,499	35.9	1,160
A. A.	82	147.3	64.6	1.57	49.6	18.5	6.81	4,106	63.6	1,854	28.7	2,252	34.9	1,430
C. B.	82	152.4	45.0	1.37	44.7	15.9	7.07	2,774	61.6	1,129	25.0	1,645	36.6	1,200
A. N.	82	151.1	62.8	1.57	37.7	13.1	6.36	3,812	60.7	1,305	20.8	2,507	39.9	1,600
E. S.	83	149.9	35.9	1.24	30.8	10.8	7.06	2,717	75.7	761	21.4	1,951	54.3	1,570
M. K.	83	152.4	53.7	1.48	35.7	13.0	6.01	2,890	53.8	939	17.5	1,951	36.3	1,320
L. W.	84	151.1	63.2	1.58	44.5	15.7	6.80	3,643	57.6	1,474	23.3	2,169	34.3	1,370
A. B.	84	147.3	65.5	1.58	39.7	13.6	7.33	4,294	65.6	1,550	23.7	2,744	41.9	1,740
M. G.	84	156.2	65.5	1.64	44.5	15.0	5.93	3,808	58.1	1,542	23.5	2,266	34.6	1,380
I. D.	85	143.5	40.4	1.26	40.0	13.9	5.76	2,973	73.6	1,083	26.8	1,891	46.8	1,500
G. B.	85	147.3	55.5	1.41	32.9	14.1	6.60	2,751	49.6	948	17.1	1,803	32.5	1,280
K. F.	89	152.4	45.5	1.38	45.0	15.1	6.22	3,330	73.2	1,362	29.9	1,968	43.3	1,430
M. W.	91	154.9	63.2	1.61	42.4	14.8	6.64	3,675	58.1	1,419	22.4	2,256	35.7	1,400
Mean	77	153.3	55.9	1.51	40.4	14.4	6.46	3,551	64.6	1,326	24.0	2,226	40.6	1,480

milliliters per kilogram of body weight, and in the case of serum volume, milliliters per square meter surface area. Table II presents similar data for 56 women, aged 70 to 91 years.

Table III is a statistical comparison of results of blood volume studies in the aged with those of Gibson and Evans for a younger group of individuals. These results are expressed in terms of liters per square meter surface area, and the data of Gibson and Evans have been corrected for difference between venous and body hematocrits.

Mean blood chemical data, serum sodium, potassium, chloride, and gamma globulin, for some of the individuals studied are listed in Table IV.

TABLE III. BLOOD VOLUME IN THE AGED: STATISTICAL COMPARISON OF RESULTS WITH THOSE OF GIBSON AND EVANS*

MEN	AGED GROUP (LITERS PER M.²)	GIBSON AND EVANS (LITERS PER M.²)
Total Blood Volume:	2.70 ± 0.053†	2.79 ± 0.043
S.D.	± 0.31	± 0.28
Red Cell Volume:	1.08 ± 0.026	1.18 ± 0.021
S.D.	± 0.15	± 0.14
Serum Volume:	1.61 ± 0.037	1.61 ± 0.028
S.D.	± 0.22	± 0.18
WOMEN	**AGED GROUP (LITERS PER M.²)**	**GIBSON AND EVANS (LITERS PER M.²)**
Total Blood Volume:	2.35 ± 0.047	2.36 ± 0.035
S.D.	± 0.36	± 0.22
Red Cell Volume:	0.88 ± 0.028	0.89 ± 0.015
S.D.	± 0.17	± 0.09
Serum Volume:	1.48 ± 0.031	1.47 ± 0.026
S.D.	± 0.23	± 0.16

*Corrected for ratio of venous:body hematocrit of 0.91.
†Mean volumes with standard errors.

TABLE IV. MEAN CHEMICAL DATA—AGED MEN AND WOMEN

SERUM SODIUM (MEQ./L.)	SERUM POTASSIUM (MEQ./L.)	SERUM CHLORIDE (MEQ./L.)	SERUM GAMMA GLOBULIN (GM. PER CENT)
148.0	4.45	103.1	0.47
(58)*	(58)	(39)	(26)

*Number of subjects.

DISCUSSION OF RESULTS

The range of blood volume in the aged group was wide, 53.4 to 88.7 ml. per kilogram in the men, and 42.3 to 92.5 ml. per kilogram in the women. For blood repletion in the older surgical patient, Beling and associates[1] have used a value of 85 ml. per kilogram of body weight. Few of the older men and women approach and fewer exceed this estimate. Means of 71.3 ml. per kilogram and 64.6 ml. per kilogram for the men and women in this study suggest that perhaps a lower figure may be more appropriate for the older age group. However, since body weight is a poor basis for comparison of blood volume data, especially in a sedentary group, all data were calculated on the basis of square meters of surface area. In Table III, such results are compared with those of Gibson and Evans for a younger group. There is close correspondence in serum volumes for older and younger men, a loss of 3.2 per cent in total blood volume, and a loss of 8.5 per cent in red cell mass in the older men. The loss in red cell mass is significant, statistically, and amounts on the

average to a loss of 170 ml. of red cells. Among the women, there is no difference in mean figures for the two age groupings. The scatter in the older group is greater, especially among the older women. This, however, was anticipated from the type of subject chosen and the method used for determining blood volume (the single ten-minute sampling). The dye method[13] and the iodinated albumin methods[7] have been shown to yield comparable results, and if difference in venous and body hematocrits is taken into consideration, such data correspond to blood volume measured by P^{32}-tagged red cells.[2, 14]

As in the younger group, there is a significant difference between blood volumes in aged men and women (13.0 per cent) and in red cell mass (18.5 per cent). For the younger group, comparable figures are 15.4 and 24.5 per cent. Thus, there is little change in the characteristic difference in blood volume between men and women in the older age group.

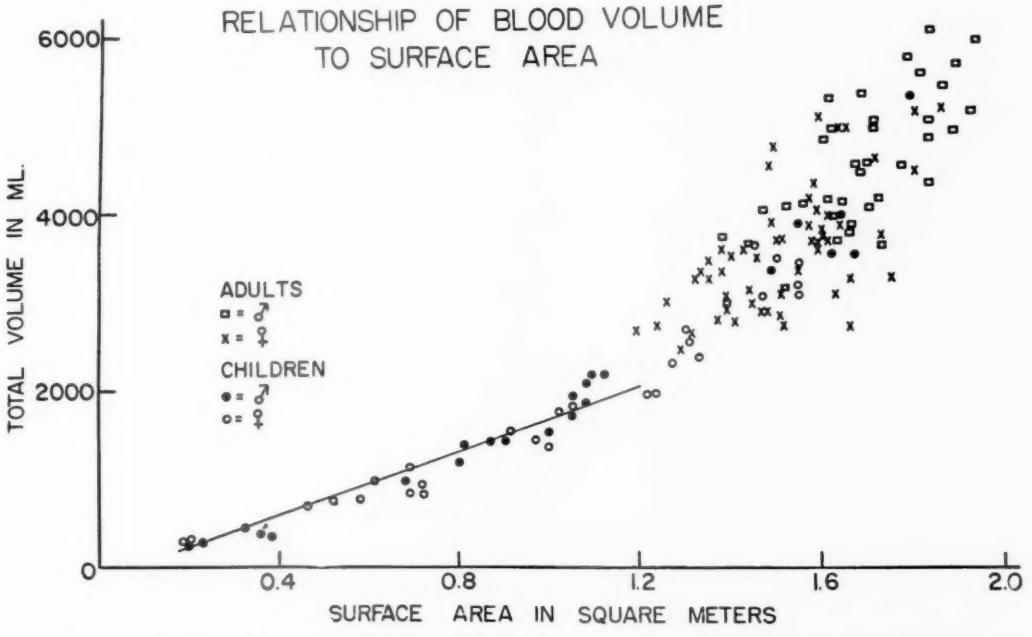

Fig. 1.—Relationship of total blood volume to surface area in aged men and women and in infants and children (data of Brines and associates,[3] 1941). Sixteen-year-old adolescents are found scattered throughout the aged group.

In Fig. 1, the total blood volume is charted against surface area for all men and women in the group studied. The points which direct the slope of the line drawn in represent blood volume data of Brines and associates[3] for infants and children. Such data were added to illustrate the change in slope which occurs at puberty and to contrast with the scatter in relationship which occurs thereafter. The nice constancy of ratio of blood volume to surface area seen in the children stops abruptly at about the age of 16. Beyond this point, differences in fat depots, muscle mass, and the lower specific gravity of women produce wide variations for both men and women. This holds for all groups: youths, adults, and the aged. In general, with increase in size or surface area, total blood volume rises steadily in both men and women. There is no evidence of a constant value in the females as reported by Gibson and Evans. It is apparent from the graph that blood volume in a given individual beyond the

age of puberty can be predicted on the basis of body weight or surface area only within wide limits.

Serum chemical findings in some of the aged individuals appear normal. There may be a suggestion of hypernatremia and reduced gamma globulin, but these data represent but half of the group.

SUMMARY AND CONCLUSIONS

1. The serum volume, and, through the hematocrit, the total blood volume and red cell mass were determined in 36 men and 56 women, aged 70 to 94 years. The Evans blue dye T-1824 was used to measure serum volume.

2. The total blood volume of aged males is greater than that of aged females. The difference is due to both the greater serum volume and even greater red cell mass in the males.

3. The greater red cell mass in the older group of men is significantly lower than that reported for the younger group by a mean value of 170 ml. of red blood cells.

4. Mean total blood volume and serum volume of both sexes and red cell volume in the older women show no significant differences from those reported for a younger group.

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SURGICAL TREATMENT AS COMPLICATED BY PRIOR ADRENOCORTICAL STEROID THERAPY

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WHEN adrenocortical steroids are employed in pharmacologic dosages therapeutically, the response of the disease state to hormone therapy is based upon its ability to influence significantly many metabolic processes,[6] blood and tissue cells[1, 8] and inflammatory tissue reactions.[2, 10] In addition to the many side effects associated with relatively short-term therapy, there is accumulating evidence that prior treatment with either ACTH or cortisone may significantly alter an individual's ability to effect necessary adjustments to a stressful situation such as an operative procedure.[3, 4, 7, 9] With the expanding use of steroid therapy, both for hospitalized and ambulatory patients, clinicians must be alert to the serious delayed consequence of shock occurring during and after even simple operative procedures of common incidence.

CLINICAL MATERIAL

During the 24-month period ending July 1, 1955, a total of 53 operations were performed on patients admitted to the Yale University Service who had coexistent or primary disease which might have warranted the administration of steroid therapy at some period of their disease (Table I). Twenty-eight patients had received steroid therapy at some time and 15 developed a shock state refractory to blood replacement during an operative procedure or immediately after operation, an incidence of more than 53 per cent. During the same interval 25 patients with the same diagnosis who had never received adrenocortical steroids were operated upon without a single episode of shock (Table I).

TABLE I

DIAGNOSIS	TOTAL CASES OPERATED UPON	STEROID GROUP		NO STEROID GROUP	
		NUMBER OPERATED UPON	NUMBER SHOCK	NUMBER OPERATED UPON	NUMBER SHOCK
Chronic ulcerative colitis	13	7	5	6	0
Splenic disease	29	15	4	14	0
Rheumatoid arthritis	8	4	4	4	0
Miscellaneous					
Adhesive arachnoiditis	1	1	1	0	0
Lupus erythematosus	2	1	1	1	0
Totals	53	28	15	25	0

In the group studied, an operative procedure was completed successfully in only two patients who had received and discontinued adrenocortical steroid therapy prior to the

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operation, one 18 months and the other 13 months before (Table II). On the other hand, in the patients who developed shock and also had discontinued cortisone therapy, the time interval varied from 3 to 24 months. Therapy with adrenocorticotrophic hormone appears to be equally as culpable since two patients who had received this agent displayed shock; one had discontinued therapy 2 months earlier and the other occurred while on continuing unchanged dosages of the trophic hormone. From these data, it appears that the total dosage, duration of therapy, and time free from steroids give no reliable information as to pituitary-adrenocortical responsivity for surviving an operative procedure.

TABLE II. STEROID GROUP

	SHOCK OCCURRED PERIOD DISCONTINUED OR CONTINUOUS		SHOCK DID NOT OCCUR AFTER DISCONTINUATION OF R
Chronic ulcerative colitis	Cortisone	3 months } one patient	Cortisone 18 months
	Cortisone	11 months }	
	ACTH	2 months	
	Cortisone	24 months	
	ACTH	continuous	
Spleen	Cortisone	continuous + depot prep.	Cortisone 13 months
	Cortisone	continuous + depot prep.	
	Cortisone	continuous + depot prep.	
	ACTH	continuous	
Miscellaneous	Cortisone	22 months	
	Cortisone	5 months	
	Cortisone	continuous + depot prep.	
	Cortisone	continuous + depot prep.	
	Cortisone	continuous + depot prep.	
	Cortisone	continuous	

It has been assumed in general that preparation for surgical procedures in patients either on steroid therapy or who had received it in the past may well be attained by preparation with depot cortisone 24 to 36 hours prior to the actual operative trauma. The dosage is a guess to meet the metabolic requirements during the period of stress. In this series (Table III) there were 6 instances of severe shock occurring among patients prepared in this fashion; 3 patients so prepared underwent the operative procedure without event. By contrast (Table III), 11 patients were prepared for operation by prior therapy with ACTH and carried through the actual procedure with this hormone. The more satisfactory results obtained by using ACTH rather than depot cortisone shown in Table III may be explained by comparing Fig. 1 with Fig. 2. In Fig. 1 are shown serial eosinophil counts taken during the course of operations on two secondarily adrenocortical insufficient patients who had been prepared for operation with depot cortisone. The two cases are sharply contrasted by their courses during operation; the one represented by the closed circles proceeded without event and was technically not difficult; the one represented by the open circles was a very difficult procedure attended by much tissue trauma

TABLE III. STEROID GROUP

	PREPARED FOR OPERATION WITH DEPOT CORTISONE		PREPARED FOR OPERATION BY ACTH, CARRIED THROUGH OPERATION WITH ACTH	
	WITH SHOCK*	WITHOUT SHOCK	WITH SHOCK	WITHOUT SHOCK
Chronic ulcerative colitis (7)	0	0	0	2
Splenic disease (15)	3	3	0	9
Miscellaneous	3	0	0	0
	6	3	0	11

*Successfully treated with intravenous hydrocortisone and blood transfusion.

and blood loss. It is evident that a high degree of adrenocortical insufficiency and severe shock were present. The operation was successfully terminated with difficulty by repeated intravenous administrations of readily soluble adrenocortical steroids.

By contrast, Fig. 2 illustrates serial eosinophil counts taken through the course of a difficult operative procedure on a secondarily adrenocortical-insufficient patient prepared for operation by ACTH and carried through the procedure with intravenous ACTH. No shock occurred.

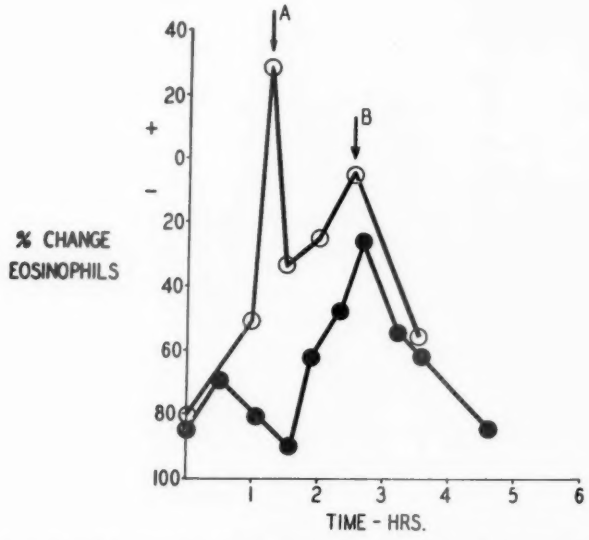

Fig. 1.—Serial eosinophil counts made during the course of operation in two patients prepared with depot cortisone. The one represented by the closed circles proceeded relatively uneventfully and was associated with minimal trauma. The one represented by the open circles was technically very difficult at the points indicated by *A* and *B*. The patient, in profound shock, was treated successfully with soluble adrenocortical steroids.

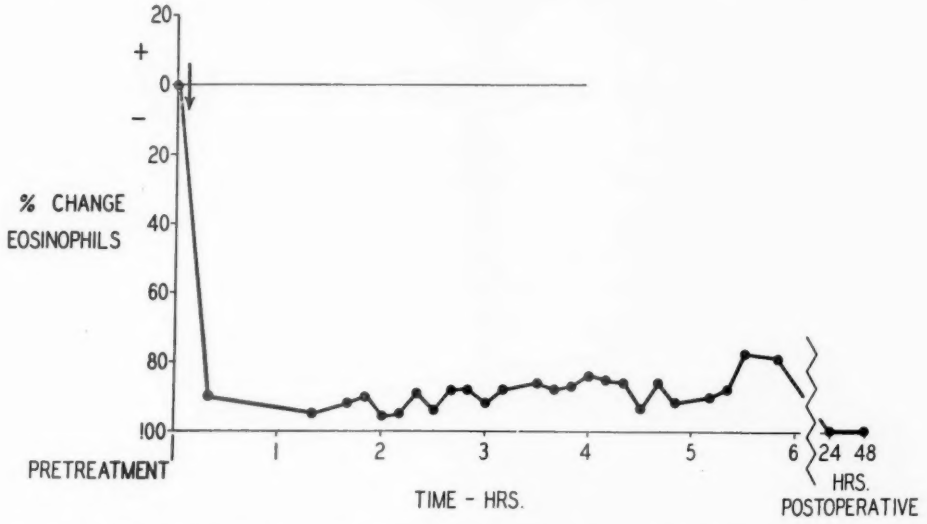

Fig. 2.—Serial eosinophil counts taken during the course of a difficult operation on a secondary adrenocortical-insufficient patient prepared and carried through the operative procedure with an infusion containing ACTH.

Cortisone acetate, minimally soluble in tissue fluids, is available at only a constant rate determined by that solubility. At any single instant the requirements for steroids arising from metabolic alterations induced by operative trauma may exceed the avail-

ability, and adrenocortical insufficiency will intervene. On the other hand, employing the trophic hormone in a continuous infusion, controlled by the clinical status of the patient, simulates the normal operating mechanisms and can maintain the availability of the steroids.

MANAGEMENT OF STEROID PATIENTS FOR AND DURING OPERATION

On the surgical service of this clinic the management of these patients resolves itself into several aspects of the problem:

When the patient is known to have received either steroid therapy or ACTH in the past but is not receiving either at the time, great importance is attached to the test measuring the eosinophil response to an eight-hour infusion of 5 per cent dextrose in distilled water containing 20 units of ACTH. An 80 per cent decrease in the eosinophil count should be present over the first four hours and a further fall to 90 per cent over the next four hours. These results constitute a positive test and indicate the existence of an adrenocortex capable of responding to ACTH. Operation is conducted without further preparation. Since in rare instances it appears[4] that even with a normal test, the fault may be an interference with the pituitary release of ACTH, a readily soluble form of adrenocortical steroid should be kept in the operating room for ready use, as the necessity may arise.

If the test is negative, that is, less than an 80 per cent fall over the first four hours, eight-hour infusions of 20 units of ACTH are repeated daily until a satisfactory response is obtained. The operation is then conducted with a constant infusion containing 20 units of ACTH per liter. The rate of administration is controlled by the anesthetist, observing the quality of the pulse, pulse rate, and level of blood pressure. The infusion is continued throughout the day of operation. For the first postoperative day the ACTH is given, 20 mg. every four hours intramuscularly. Each subsequent day a single alternate dose is omitted, simulating the gradual physiologic decrease in pituitary ACTH release that occurs in normal convalescence. It should be emphasized that postoperative complications will increase the requirements for steroids and should be managed with increasing amounts of the trophic hormone, if and when they occur.

When the patient is receiving ACTH at the time of operation, the operation and postoperative period is managed directly as described above.

When the patient is receiving adrenocortical steroids at the time of operation, daily eight-hour ACTH infusions are administered as the steroid is gradually withdrawn, usually requiring three to five days. This conversion is followed closely by the four- and eight-hour eosinophil counts. When adequately prepared, the operation and convalescence is managed as outlined above.

An alternative procedure to all these, considered less satisfactory because of the limited availability of the steroid, is the use of depot cortisone. If this method is chosen, readily soluble forms of steroid supplements must be at hand in the operating room.

A serious situation arises *when the patient is not known to have received steroid therapy until shock occurs,* usually during the operative procedure. The existence of relative adrenocortical insufficiency contributory to the shock is strongly suggested[5] when the shock is inconsistent with the magnitude of the operative procedure or is irreversible to a clinical estimate of adequate blood replacement. If possible, an eosinophil count should be done at once; if it is more than a very low figure (10 to 15 per cubic millimeter), steroid therapy should be started at once. If facilities for doing the eosinophil count are not available, a therapeutic trial of steroid administration should be given. It is advised that 200 mg. of hydrocortisone be given intravenously as rapidly as possible. The blood pressure response is dramatically rapid, if adrenocortical insufficiency is present. Maintenance for the remainder of the operation is obtained by giving 200 mg. of the steroid in each 500 c.c. of blood. Convalescence is managed by a tapering schedule of the soluble steroid given intramuscularly at frequent intervals over the next three to five days.

SUMMARY

Experience in a surgical clinic with steroid-induced adrenocortical insufficiency has been reviewed. It is becoming a serious complication which all physicians should anticipate by recording in the routine history whether a candidate for operation has ever received ACTH or adrenocortical steroid therapy. Duration since discontinuing the drug, dose employed, and duration of treatment given no reliable data concerning the patient's ability to withstand an operation.

A program of management under the varying clinical circumstances associated with this program has been offered employing ACTH, depot cortisone, or soluble steroids. This clinic's preference for ACTH has been outlined with the reasons for its choice.

ADDENDUM

Since this paper was submitted, the availability of soluble steroids has offered another program of management which this clinic has found to be equally as satisfactory as ACTH:

ELECTIVE OPERATION

Preoperative Day 1.—Cortisone 50 mg. IM in each of 4 sites at 6 P.M. (total 200 mg.).

Operative Day.—(a) Hydrocortisone 50 mg. IM in each of 2 sites just before premedication (total 100 mg.). (b) Hydrocortisone 100 mg. in each 500 c.c. of blood or fluids

WITHDRAWAL SCHEDULE

	HYDROCORTISONE (mg. IM q. 6 h.)	ACTH				
Postop. Day 1	50	IV 15 mg. in 1 liter 5% DW to run 8 hours				
			6 A.M.	12 N.	6 P.M.	12 M.
Postop. Day 2	40	IM	15	15	15	15
Postop. Day 3	30		15	15	15	0
Postop. Day 4	20		15	0	15	0
Postop. Day 5	10		15	0	0	0
Postop. Day 6	0		0	0	0	0

during operation. Note: Patient should come to the operating room with 6 ampules of hydrocortisone (100 mg. each). (c) At completion of operation, hydrocortisone 100 mg. IM.

SUGGESTED PLAN FOR EMERGENCY OPERATIONS

This is less satisfactory and should be used only when the delay caused by the elective schedule would interfere with the urgent nature of the operation.

1. Hydrocortisone 100 mg. IM in each of 4 sites prior to operation.
2. Hydrocortisone 100 mg. in each 500 c.c. of fluid or blood.
3. Hydrocortisone 6 ampules in OR for anesthetist.
4. Hydrocortisone 100 mg. IM at end of operation.
5. Effect withdrawal as for elective procedures.

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ELECTROCARDIOGRAPHIC CHANGES IN ACUTE PANCREATITIS

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DURING the course of a series of observations on the role of trypsin in the pathogenesis of the local and systemic lesions of acute pancreatic necrosis, information was sought on the possibility of tissue changes characteristic of trypsin action. The striking local changes found in acute pancreatitis are tissue necrosis, vascular medial necrosis and hyalinization (Rich and Duff[10]), fat necrosis, and hemorrhage. These investigators were able to reproduce these lesions, with the exception of fat necrosis in the subcutaneous tissues, by the subcutaneous injection in dogs of the proteolytic enzyme papain, crude trypsin, crystallized trypsin (Northrop and Kunitz[8]), and pancreatic juice which was rich in trypsin. In our own experiments with rabbits (unpublished observations) we have produced all the lesions by intraperitoneal injection of crude trypsin, and all the lesions apart from fat necrosis by intraperitoneal injection of crystalline trypsin.

The more severe forms of human acute pancreatitis are accompanied early in their course by a profound state of collapse. This state has been shown by Elliott[4] to be associated with a depletion of the blood volume which he considers sufficiently severe to account for the syndrome. It was in order to elucidate other possible factors in this state that the following investigation was made. In particular we were concerned to discover whether there is early evidence of liberation into the blood stream of abnormal substances, perhaps enzymes, from the destroyed pancreas, and the effects on the heart.

METHODS

Recently fed mongrel dogs were anesthetized with pentobarbital sodium (veterinary Nembutal), 30 mg. per kilogram intravenously, and the abdomen opened. The accessory pancreatic duct was cannulated by the method of Rich and Duff[10] and 8 to 10 c.c. of bile aspirated from the animal's own gall bladder was injected with maximum force (exceeding 80 cm. of water) into the duct. The pancreas was observed to become bile stained, then swollen and hemorrhagic before the abdomen was closed. In ten animals femoral arterial pressure was recorded by means of a polyethylene catheter in the femoral artery connected to a capacitance manometer.

During the course of these investigations certain interesting electrocardiographic features were noted. In order to evaluate these findings, electrocardiograms consisting of the three standard leads, were taken under the following conditions: (1) in normal dogs under pentobarbital sodium anesthesia; (2) before, during, and after the production of acute hemorrhagic pancreatic necrosis; (3) before, during, and after abdominal operations,

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unrelated to the pancreas; (4) before and during hemorrhagic shock; (5) before and for two to three hours following intravenous injection of crystalline trypsin; (6) before and after intravenous injection of beta chymotrypsin; (7) before and after intravenous injection of normal pancreatic juice, sterile and unsterile.

At autopsy in all animals the apex of the left ventricle and a piece of diaphragm were excised, and sections were cut and stained with hematoxylin and eosin.

RESULTS

A. Electrocardiographic Features.—

1. The normal dog electrocardiogram under pentobarbital sodium anesthesia and the changes which occur as the dog recovers from the anesthetic: Twenty-seven adult mongrel dogs were studied. Thirty milligrams of veterinary Nembutal per kilogram of body weight was injected intravenously, after which three limb-lead electrocardiograms were taken at intervals over a period of one to three hours with the dog strapped on an operating table in supine position.

a. Rate: The heart rate varied from 94 to 266 per minute, tending to increase with recovery of the animal from the anesthetic. Most of the rates fell between 140 and 200 per minute.

b. Rhythm and axis: in all the rhythm was sinus and the axis nearly vertical.

c. P-R interval varied from 0.07 to 0.14 seconds, being fairly constant for each dog and inversely related to the heart rate.

d. QRS was remarkably constant at 0.03 to 0.04 second: only one dog showed a duration of 0.05 second.

e. P waves: In all dogs, the P wave in Leads II and III was positive, tending to increase in amplitude as the dog recovered from the anesthetic. In different dogs it varied in height from 0.1 to 0.9 mv. In Lead I, P was frequently inverted or flat. P was usually equal to or greater than T in Lead II.

f. T waves: The T wave was usually positive in Leads II and III, although occasionally flat or slightly inverted. While the dog was still fairly deeply anesthetized the inversion was not greater than 0.1 mv., but when the anesthetic lightened, on three occasions a positive T wave in Leads II and III was replaced by a negative T wave of 0.2 to 0.25 mv. In Lead I T was frequently negative.

g. S-T segment: In nearly half the dogs in Leads II and III this segment was depressed below the isoelectric line established by P-Q. This depression was usually only 0.05 to 0.1 mv. and never exceeded 0.15 mv.

h. T-P segment: When the rate was rapid the T wave sometimes did not return to isoelectric before the start of the next P wave. This elevation of the T-P segment occurred in less than one fourth of the dogs and never amounted to more than 0.15 mv.

2. Electrocardiographic changes during and after experimental production of acute hemorrhagic pancreatic necrosis: Twenty-six dogs were studied, of which 19 died within 36 hours. The remaining 7 survived to be sacrificed at various times after one week. In all the animals which died as a result of

pancreatitis the body of the pancreas was found to be completely destroyed by hemorrhagic necrosis, although the descending process usually escaped. In the survivors fibrosis was the dominant feature in the pancreas.

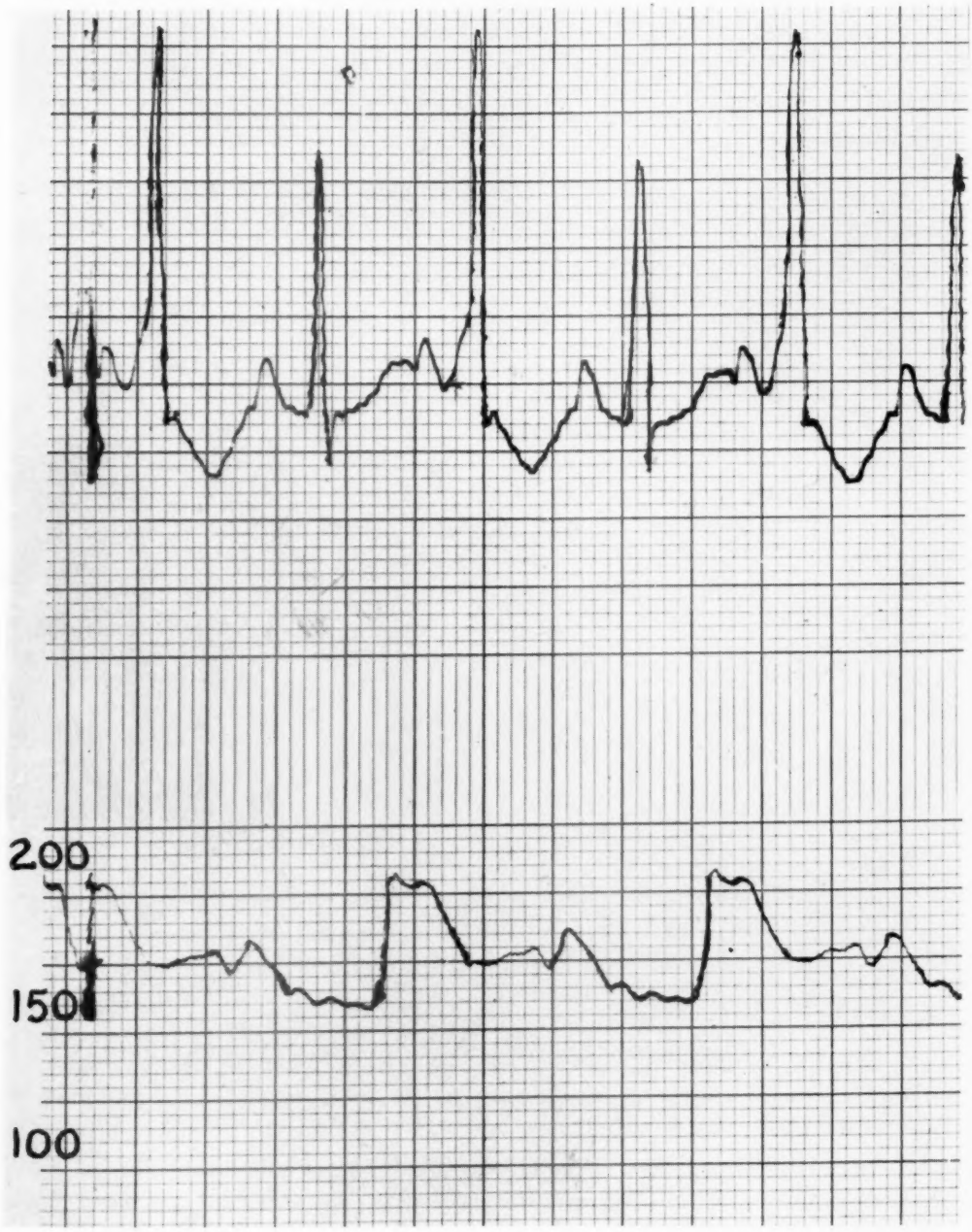

Fig. 1.—Wolff-Parkinson-White syndrome in alternate beats five minutes after production of acute pancreatitis. Note the mechanical pulsus alternans revealed by the femoral artery pressure tracing.

In 16 dogs, 5 of which survived, no significant changes were found in the electrocardiogram.

In one dog which died, P became inverted in Leads II and III after five minutes and remained so during the three hours of observation, indicating that the pacemaker had shifted to the A-V node.

One dog which survived the procedure temporarily showed alternate "accelerated conduction" of the Wolff-Parkinson-White syndrome (Fig. 1). We were recording arterial blood pressure at the time and the mechanical pulsus alternans is clearly seen. This disturbance was found only in the record taken five minutes after injection of bile. The record was substantially normal

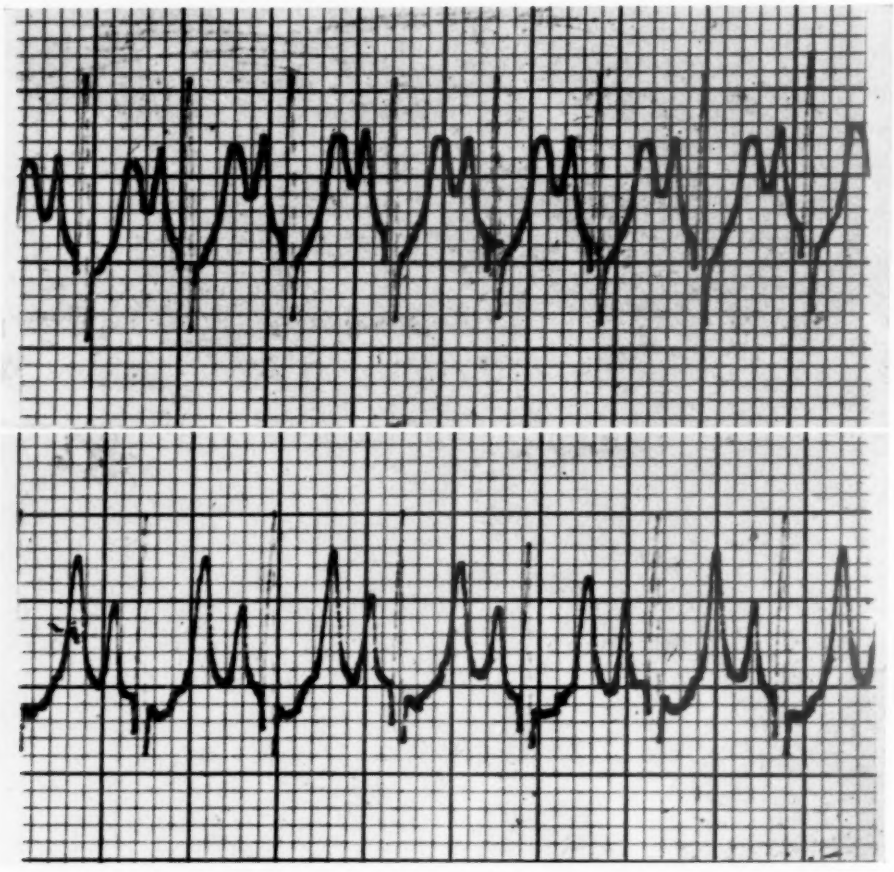

Fig. 2.—Pancreatitis. ECG record, Lead II, before (above) and two hours after (below) the production of acute pancreatitis. Note the upright spiking of the T wave.

five minutes later, and for the three hours of observation. When a final record was taken just before the dog was sacrificed on the twelfth day, no significant abnormality was seen.

The change most often seen was in the T wave in leads II and III. In 3 dogs T increased in amplitude and became spiked (Fig. 2). In one this change was seen within ten minutes of injection of the bile and the dog died within fifteen minutes. The other 2 dogs died within 24 hours.

In 5 dogs, of which one survived, the striking change was an inversion of T exceeding 0.2 mv. in Lead II (Fig. 3). This occurred within 30 minutes of in-

jection of the bile and persisted during the two to three hours of examination. In the surviving dog T was still inverted in Lead II when the dog was sacrificed a week later, and S-T was depressed 0.2 mv. below isoelectric.

3. Electrocardiographic changes as a result of other abdominal operations: Electrocardiographic records were made under Nembutal anesthesia in 5 dogs during and after the substitution of a gastric pouch for the colon, and in one dog during and after the construction of a duodenal pouch. In none of these dogs were significant electrocardiographic changes found.

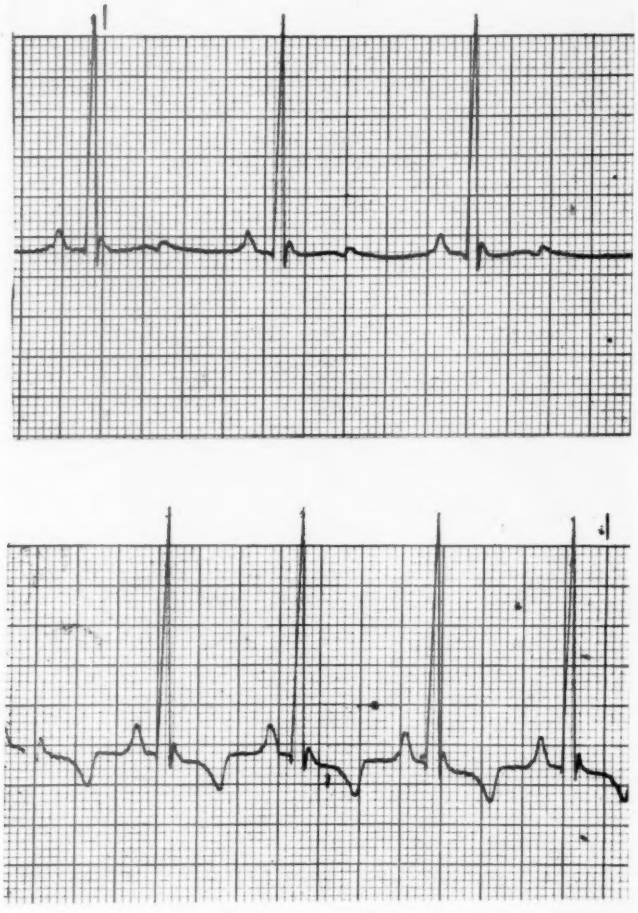

Fig. 3.—*A*, Lead II before operation. *B*, Lead II thirty minutes after injection of bile into accessory pancreatic duct. The T wave is steeply inverted.

4. Hemorrhage: Electrocardiographic records were made on 5 dogs before, during, and after production of hemorrhagic shock by removal of 450 c.c. of blood (approximately 35 to 40 per cent of blood volume) under Nembutal anesthesia. In all there appeared a depression of ST in Leads II and III of 0.15 to 0.18 mv. amplitude. No change was seen in P or T waves.

5. Intravenous trypsin: Electrocardiographic records were made under Nembutal anesthesia on 6 dogs after intravenous injection of 25 to 50 mg. crystalline trypsin per kilogram. In 4 dogs no significant change was found, and

in the other 2 there occurred an increase in amplitude of the T wave and a change of shape so that it became spiked (Fig. 4). In none was T wave inversion produced.

6. Intravenous chymotrypsin: In 2 dogs under Nembutal anesthesia intravenous injection of 100 mg. tyrosine-equivalent of beta chymotrypsin produced no electrocardiographic changes.

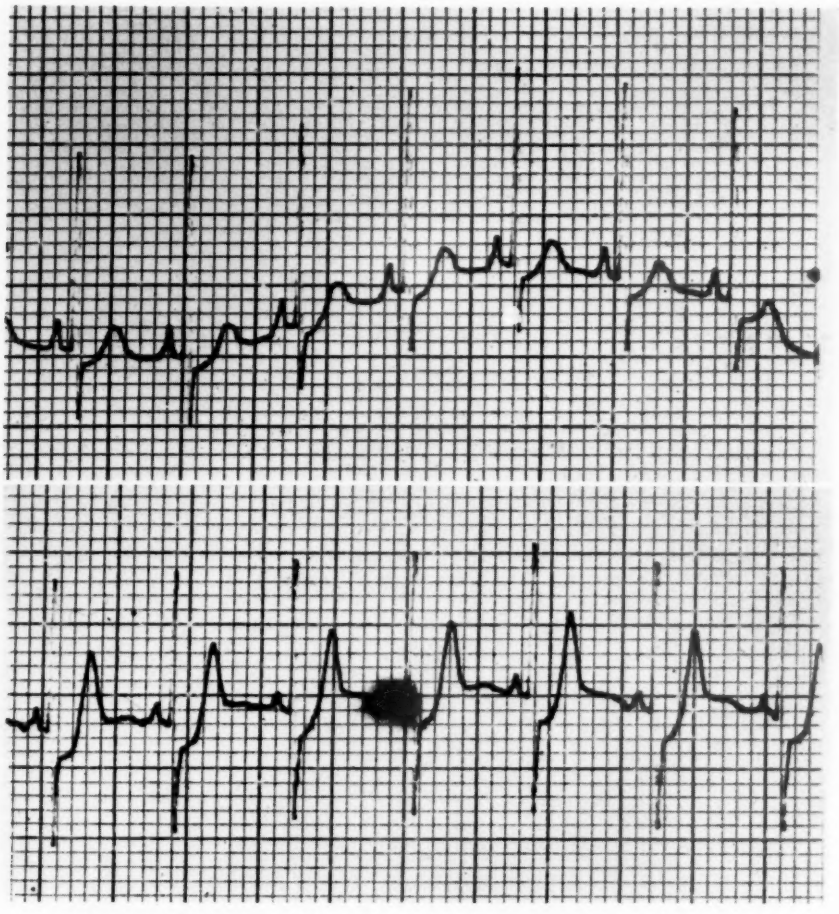

Fig. 4.—Intravenous trypsin. ECG record (Lead II) before (above) and two minutes after (below) intravenous injection of crystalline trypsin 30 mg. per kilogram body weight. Note the upright spiking of the T wave.

7. Intravenous pancreatic juice: In 7 dogs under Nembutal anesthesia intravenous injection of 10 c.c. of unsterile pancreatic juice collected from a dog with a Dragstedt pancreaticoduodenal fistula was tolerated. In two there was no disturbance apart from tachycardia, in 2 the T wave in Leads II and III increased in amplitude and became spiked in an upright direction (Fig. 5), and in the remaining 3 T became steeply inverted in Leads II and III (0.2-0.5 mv.).

Six dogs under Nembutal anesthesia were then injected with similar amounts of pancreatic juice collected in the same way but sterilized by Seitz filtration before injection. In none of these 6 dogs was there inversion of T but in 2 of

them T in Leads II and III increased in amplitude in an upright direction and became spiked. Similar changes were seen sometimes after injection of crystalline trypsin and in 3 dogs with pancreatitis.

B. Blood Pressure Changes Following Experimental Acute Pancreatitis.—In 10 dogs in which the blood pressure was recorded before and after the experimental production of acute pancreatitis there occurred at most a very mild hypotension within the first two hours. In none did the blood pressure fall below 120/75 mm. Hg. A transient pulsus alternans was found in 2 dogs, of which

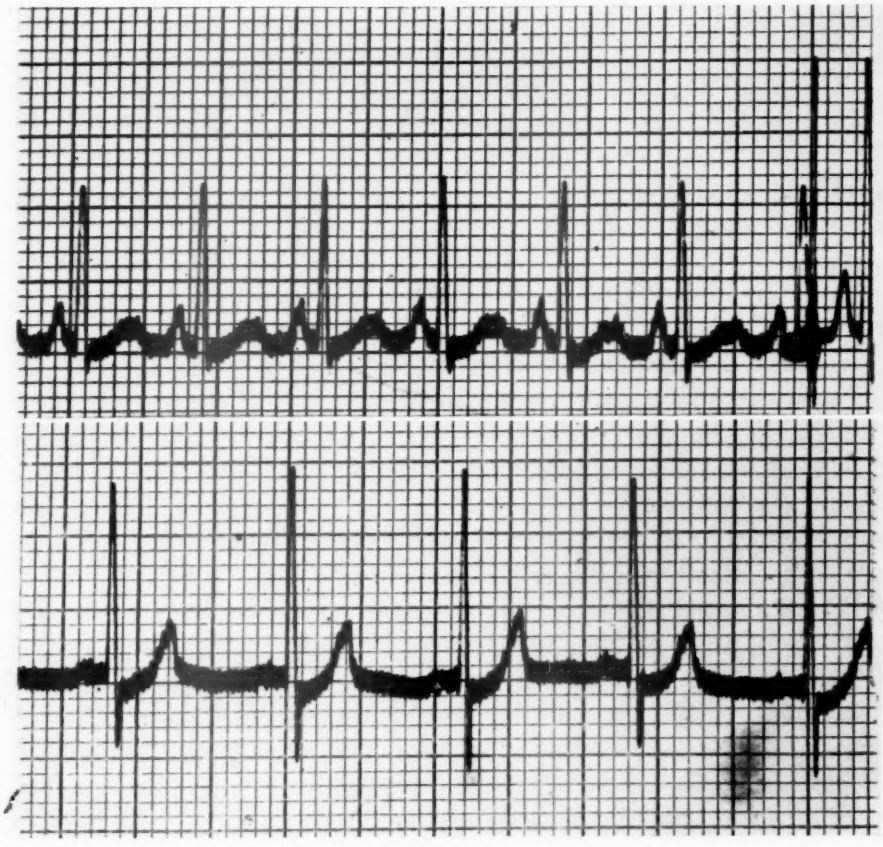

Fig. 5.—Sterile pancreatic juice. ECG record (Lead II) before (above) and after (below) intravenous injection of 10 c.c. sterile pancreatic juice. Note the upright spiking of the T wave.

one showed a normal electrocardiogram and the other a transient Wolff-Parkinson-White syndrome. There was no evidence that the electrocardiographic abnormalities found in 10 dogs were related to shock.

C. Histological Changes in Cardiac and Skeletal Muscle as a Result of Experimental Pancreatitis and Intravenous Injection of Pancreatic Juice, and Trypsin in Dogs.—In none of 20 dogs (including those with electrocardiographic changes) which died or were sacrificed after experimental production of acute pancreatitis was there gross or histological evidence of focal necrosis, thrombosis, hemorrhage or vascular changes in sections of left ventricle or diaphragm. Similarly no changes were found in 11 dogs after intravenous injection of trypsin or pancreatic juice.

DISCUSSION

Abnormalities were found in 10 out of 26 dogs studied electrocardiographically after experimental production of acute pancreatic necrosis. These abnormalities were confined to changes in rhythm and changes in repolarization. In particular no Q waves, axis change, or conduction block were found.

Changes in Rhythm.—In one dog the pacemaker shifted to the A-V node five minutes after injection of bile into the pancreatic duct and remained so. In a second dog the Wolff-Parkinson-White syndrome was found temporarily five minutes after injection of bile. In this animal the alternate abnormal beats were mechanically inefficient as judged by the lower arterial pressure associated with them (Fig. 1). The Wolff-Parkinson-White syndrome has been reproduced experimentally by direct cardiac manipulation. For example, Butterworth and Poindexter[2] produced it by amplifying the auricular electrical activity and leading it into the ventricle. Prinzmetal and associates[9] caused the pattern by subthreshold stimulation in the region of the atrioventricular node. It has also been reported by Lieberman, Taylor and Wright[7] in a rabbit after intravenous infusion of crystalline trypsin. We did not find it in any of our dogs injected with trypsin or pancreatic juice.

Changes in Repolarization.—In 5 animals the shape and direction of the T wave became abnormal soon after injection of bile into the pancreatic duct and in 3 others the shape and size only became abnormal. Similar changes were found in 7 out of 13 animals following intravenous injection of pancreatic juice.

That these effects are in fact due to liberation into the blood stream of pancreatic proteolytic enzymes is suggested by a body of clinical and experimental work. Electrocardiographic changes in ST and T segments, sometimes suggestive of myocardial infarction, have been reported in patients with acute hemorrhagic necrosis of the pancreas by Dittler and McGavack,[3] Bauerlein and Stobbe,[1] and Gottesman, Casten, and Beller.[5] The last-named authors found electrocardiographic changes in 5 dogs with experimental acute pancreatitis but no gross or microscopic evidence of myocardial damage at autopsy.

Vogel[12] published unique autopsy findings in a hypertensive woman of 44 who died of acute hemorrhagic pancreatitis three days after a left thoracolumbar sympathectomy. Apart from the local lesion he found changes in the brain, heart, adrenals, and possibly in the right ovary. In the brain he found focal areas of demyelination. "The myocardium contained scattered minute greyish-red streaks; these on histological section were formed of focal groups of muscle cells in which there were a striking loss of sarcoplasm and an absence of pyknosis of nuclei. In contrast, the reticulum and collagenous interstitial tissues remained intact and appeared as delicate honeycomb structures that were slightly infiltrated by lymphocytes and small mononuclear phagocytes." The appearance in the adrenals and possibly the right ovary was similar. He considered that the changes might be due to circulating trypsin, pointing out that Robb-Smith[11] had incubated lipase and trypsin with human skeletal muscle. Lipase caused no histological changes apart from some loss of cross striation, while trypsin caused disappearance of the sarcous substance without influencing the reticulin or collagen fibers.

Kellner and Robertson[6] produced selective necrosis of cardiac and skeletal muscles by intravenous injection of proteolytic enzymes in rabbits. The lesions were strikingly similar histologically to those described by Vogel. They produced these characteristic lesions in 10 out of 13 that survived injection of crude trypsin, and 3 out of 4 that survived injection of crystalline trypsin. The lesions were not produced if 100 mg. of crystalline soybean trypsin inhibitor was injected immediately before the trypsin.

The same authors found electrocardiographic changes "in the ST segment and abnormal T waves" ten minutes after injection of the proteolytic enzyme. These changes became striking 30 to 60 minutes later in rabbits in which myocardial lesions were subsequently found.

Lieberman, Taylor, and Wright confirmed and extended these findings in rabbits. They found electrocardiographic changes in 19 out of 24 rabbits successfully infused at the rate of 0.2 to 1 mg. per minute with crystalline trypsin intravenously. In 12 animals they found changes in the P wave, which tended to increase in amplitude and the axis of which deviated to the right. Changes in the QRS complex occurred in 10 animals, and in 16 animals there were changes in the ST segment (commonly depression, with a concavity toward the isoelectric line) and in the T wave (marked variation in the height, direction, and shape).

CONCLUSIONS

In 8 out of 26 dogs studied electrocardiographically after experimental production of acute pancreatic necrosis, changes were found which were similar to those produced by intravenous injection of pancreatic juice in dogs.

These changes were not found only in the more lethal cases of pancreatitis, as 11 dogs died of the 16 whose electrocardiograms remained normal, and there was one survivor of the 8 with T wave changes. We have no explanation for the absence of changes in so many of the dogs, both with pancreatitis and after injection of trypsin or pancreatic juice. The changes are not due simply to diminished blood volume as they were not found in dogs after hemorrhage and hypotension was not associated with the pancreatitis. The response to intravenous pancreatic juice suggests that the electrocardiographic changes are due to some substance from the pancreas entering the blood stream. We have not been able to show any histologic changes in the myocardium such as Kellner and Robertson[6] have shown in rabbits, but it is likely that this is a species difference. The latter authors were unable to confirm their findings in chickens or guinea pigs.

SUMMARY

1. Electrocardiographic changes, notably in the T wave, were found in 10 out of 26 dogs with experimental acute hemorrhagic pancreatic necrosis.

2. In one dog alternate Wolff-Parkinson-White complexes were found.

3. Similar changes were seen in 7 of 13 dogs following intravenous injection of pancreatic juice, and in 2 of 6 after injection of crystalline trypsin.

4. No histologic evidence of focal myocardial necrosis was discovered.

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CRANIOSYNOSTOSIS

A Modification in Surgical Treatment

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PREMATURE closure of cranial sutures in infants and children is a disorder of obscure etiology which has continued to present an intriguing surgical problem since the era of Lane[9] and Lannelongue[10] (1890). Classification, diagnosis, and treatment of the various types of craniosynostosis were carefully appraised by Faber and Towne,[2, 3] who clarified the critical features of this syndrome, outlined a sound technique for surgical treatment, and strongly advised that operation be carried out as early as possible to provide sufficient room for the rapidly growing youthful brain. These fundamental views have later been enlarged upon and re-emphasized by others.[4, 7, 11, 12]

Craniosynostosis was originally classified clinically by appearance of the deformed head, a system of grouping which involved many picturesque but sometimes confusing terms. Because the pathologic process may involve one or combinations of the cranial sutures, the old names have been largely discarded in favor of direct x-ray identification of the suture or sutures involved. That is, "sagittal synostosis" is used rather than "scaphocephaly," and so forth. Unusual head contour should, however, alert the observer to the possibility of premature suture closure, and suggest which of these may be involved before roentgenograms are taken. The vault cannot enlarge at right angles to a fused suture, and closure of the sagittal suture, for example, causes the calvarium to be narrow and long, whereas fixation of the coronal suture produces shortening and broadening of the head. These features have been very ably presented in the past[6] and will not be enlarged upon here.

Growth of the human brain is particularly rapid in the first 2 years of life and is nearly complete at the age of 5 years, yet cranial vault sutures do not ordinarily fuse before the age of 50. As the cerebrum enlarges new bone is laid down at the sutures thereby broadening bones of the vault and increasing capacity of the skull in accordance with brain growth. Too-early fusion of skull sutures will restrict bone growth, bring about deformity and reduced capacity of the brain case, and may cause cerebral compression and increased intracranial pressure manifested by vomiting, lethargy, mental retardation, blindness, or other serious sequelae. Operations for craniosynostosis have two important objectives: the prevention of these potential complications, and improvement in contour and proportion of the patient's head.

Superficially similar is the picture seen in microcephaly, a state wherein cerebral growth is primarily retarded and the head fails to enlarge on this

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account. It is essential that distinction be made between this and the totally unrelated condition of premature suture closure, avoiding needless surgery in the microcephalic child.

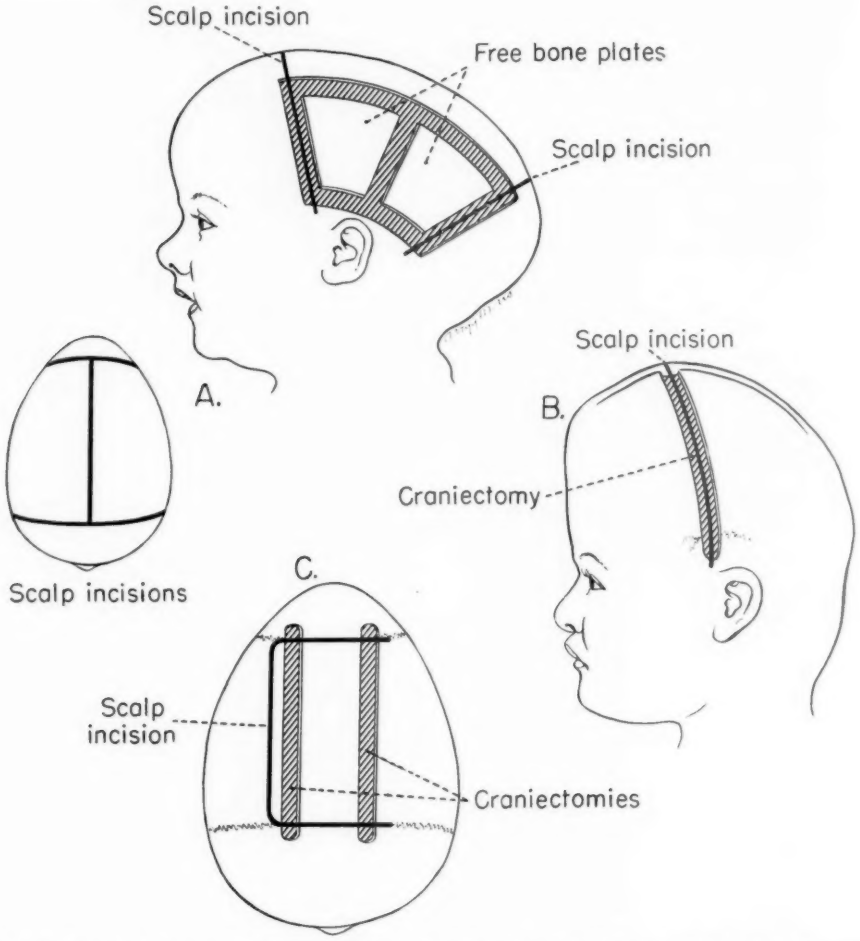

Fig. 1.—Surgical treatment of craniosynostosis. *A*, Recommended scalp incisions and craniectomies for sagittal synostosis (scaphocephaly) in children more than 12 months of age. Free bone flap are cut bilaterally, reaching beyond coronal and lambdoid sutures. *B*, Coronal synostosis. Craniectomy is carried across squamosal suture. *C*, ⊏- shaped scalp incision and parasagittal craniectomies employed in treatment of sagittal synostosis in infants. Bone cuts cross lambdoid and coronal sutures.

Various modifications in craniectomy for craniosynostosis have been evolved, leading to the current basic method of providing for cranial expansion, namely, wide resection of pericranium followed by cutting of linear channels, 1 to 1.5 cm. wide through both tables of the skull along the axis of the fused suture or sutures.[6] In sagittal synostosis (scaphocephaly), two parasagittal channels are made leaving a midline strip of bone intact to protect the longitudinal sinus; the parasagittal cuts must extend into frontal and occipital bones, crossing coronal and lambdoid sutures, respectively. Coronal synostosis (brachycephaly) is treated by craniectomy adjacent to this suture, reaching from the temporal squama across the squamosal suture to the midline in the case of unilateral fusion, or continuing across and downward to the opposite squamosal bone when bilateral synostosis is present

(Fig. 1). The same principles apply to lambdoid synostosis or various combinations of fusion, such as sagittal plus coronal, sagittal with lambdoid, and so forth.

When all sutures are closed (oxycephaly), the cuts must extend along coronal, squamosal, lambdoid, and parasagittal regions forming an unattached plate on each side and along the midline, each of which may be divided transversely to improve contour (Fig. 2). We have been disappointed by results of linear parasagittal craniectomies for sagittal synostosis in children older than 1 year, and now advise that a free bone flap be cut on each side to permit maximum cranial growth and most satisfactory contours, this procedure being done in two stages using transverse "H"-shaped skin incision (Fig. 1, *A*).

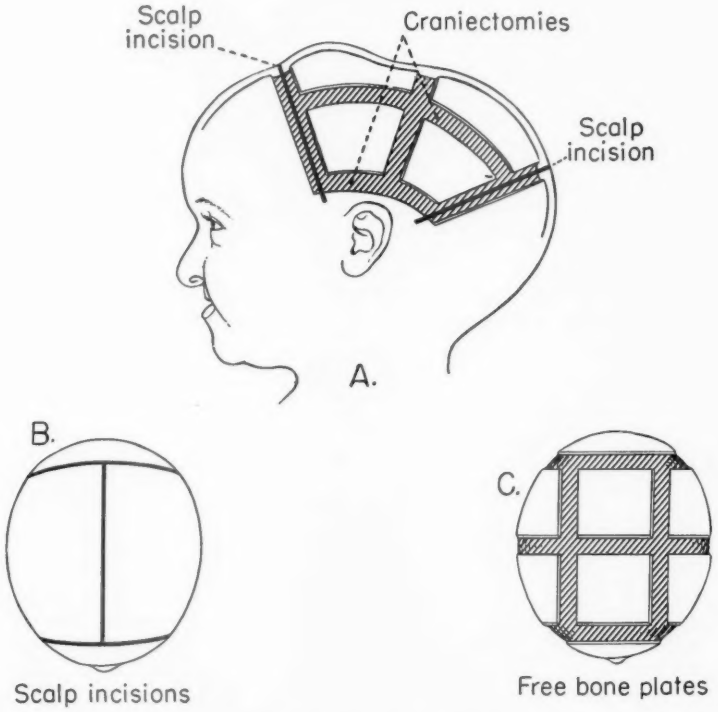

Fig. 2.—Fusion of all cranial sutures (oxycephaly). Scalp incisions and free bone plates are shown.

Earlier craniectomy operations allowed for immediate enlargement of the skull and theoretically offered the needed elasticity to accommodate brain growth, but it was soon found that rapid regeneration of bone usually occurred, sometimes producing solid fusion of channels in four to six months.[6, 16] Because of this, secondary operations were frequently required to relieve recurrent symptoms of intracranial hypertension, and to obtain optimum cosmetic result. To combat this serious deficiency of the existing surgical method, Ingraham and associates[5] evolved a technique which has since become standard and has greatly enhanced results of surgical therapy in craniosynostosis. These workers showed experimentally that regrowth of bone across craniectomy channels in monkeys was remarkably retarded if periosteum was removed and the bone edges encased with tantalum foil, acrylic,

polyethylene tubing, or polyethylene film. Film was found to be technically most practical and was selected as the choice for clinical use. Simmons and Peyton[16] previously reported the use of tantalum foil in two patients, and were the first to record clinical application of a regrowth-delaying technique. Later reviews of several authors' experience with the polyethylene film method have been favorable and shown that it is reliable and generally very satisfactory.[4, 7, 11]

The first five cases so treated in our hospital progressed much more favorably than had patients with simple craniectomy, and no complications developed. However, the next patient exhibited early intolerance to the polyethylene film and, in due course, two operations were required to remove film from both parasagittal cuts and secure wound healing. (In a later patient, reaction to film necessitated its removal twelve months after surgery.) This unfortunate situation prompted search for a different method of retarding new bone formation and it was hoped also to develop a simpler, effective technique, since placement of film had in some instances been rather tedious.

To reduce osteoblastic potential of the external layer of dura mater, topical application of various agents was carried out with the objective of partially destroying this layer, thereby inhibiting regrowth of bone. The first patient was treated cautiously, 1.75 per cent tincture of iodine being applied to a selected area of dura exposed by craniectomy. Subsequent skull roentgenograms in this and another similarly treated patient showed that bone regeneration was not influenced and, accordingly, 3.5 per cent tincture of iodine was used in two patients with sagittal synostosis, this solution being placed on the dura in the right channel, the left dura undisturbed. Periodic x-rays showed moderate difference in rate of new bone formation up to two years, the treated side remaining open longer.

These partial successes led to our present method for delaying regeneration of bone after craniectomy, namely, the application of Zenker's-acetic fixative solution or "strong" (7 per cent) tincture of iodine to the exposed dura mater throughout the length of the craniectomy channel. Since November, 1952, this method has been employed in a total of 36 patients, 30 of whom have been followed for more than six months since operation. In 3 of the latter group with sagittal synostosis, the dura in one channel was treated, in the other side, untreated. In 12 others, polyethylene film was secured to the bone margins of craniectomy on one side of the skull and tincture of iodine used on the dura on the other side. In ten, Zenker's-acetic was applied to one channel, iodine forte to the other. Pericranium was widely removed in all instances and bone openings were cut as nearly symmetrical as possible.

Careful appraisal of skull roentgenograms taken at six-month intervals after all of these operations demonstrated that the chemically-treated channel remained open much longer than unmodified craniectomies usually do (Fig. 3), and the rate of closure by bone regeneration was roughly parallel to the film-bearing channel. In a few cases, the iodine side appeared to close a little more slowly than the film-treated channel, especially in the early months; in others, the result at twelve months favored the film side by a slight margin. Bone regenerating from the dura mater could be seen by roent-

genogram along the film-protected craniectomy about six months after surgery, but although a sturdy-looking strip of bone was gradually laid down, narrow radiolucent streaks persisted at each side of this along the course of the film (Figs. 4, 5, and 6). In later stages, bone appeared to grow beneath and above the film, resulting in solid fusion. Results of the comparative survey between Zenker's and iodine thus far show maintenance of wider craniectomy and slower bone regrowth on the Zenker's-treated side.

Fig. 3.—Posteroanterior roentgenogram of skull six months postoperatively in a 4½-year-old boy with sagittal synostosis. Dura in right craniectomy treated with 7 per cent iodine tincture, left craniectomy ronguered identically but no other treatment added. There is pronounced difference in bone regeneration, the unmodified channel on the left showing well-advanced fusion. More extensive operation is now advised in children older than 1 year (Fig. 1, *A*).

Unaccountable variations occur in the regenerative process. For instance, one will occasionally find remarkably slow regrowth of bone in craniectomies not treated with polyethylene film or other delaying method, as illustrated by a 6-month-old patient in the present series whose skull roentgenograms demonstrated clearly defined channels two years after performance of simple craniectomies. Because of this variability in rate of new bone formation among individuals of similar age, and also between different regions of any one cranium, one must assess craniectomy techniques with caution, and in an adequate number of cases. However, certain tentative con-

clusions may be drawn, as follows: (1) Unmodified craniectomy channels will usually be fused by new bone formation and be nonfunctional six months after operation, especially in infants less than 1 year old. (2) Encasing the bone edges with polyethylene film definitely retards closure of craniectomies, rendering them functional for two years or more in most instances. (3) Treating the dura mater in the craniectomy opening with 7 per cent tincture of iodine has in the present series delayed new bone formation to about the same degree and Zenker's-acetic solution is probably even more effective. (4) As a corollary to (3), it is likely that the dura in infants and young children forms new bone at least as efficiently as does the pericranium.

A. *B.*

Fig. 4.—*A*, Seventeen-month-old boy with sagittal synostosis. Anteroposterior view of skull eight months after operation, when bilateral parasagittal craniectomies were performed and the dura insufficiently treated with 7 per cent iodine, this solution being applied very sparingly. Surgical openings appear almost obliterated by new bone, and solid fusion was found at second operation. *B*, Same patient eleven months after second craniectomy. At reoperation, dura on left was thoroughly treated with 7 per cent iodine (see text), and polyethylene film affixed to right bone edges. New bone arising from dura is evident on right side, but both channels have widened due to expansion of the cranium, and are considered functional.

It must be stressed that the effectiveness of the Zenker's-acetic method depends upon the concentrated solution remaining in contact with all portions of the exposed dura mater in the craniectomy opening for five minutes; short or scanty application is valueless. If iodine forte is used, it should remain on the dural surface for at least seven minutes. Bone margins should be waxed if necessary beforehand, and all dural bleeding points checked with cautery to provide a perfectly dry field. The solution* is then brushed on generously

*Zenker's-acetic solution is prepared by mixing Zenker's fixative with glacial acetic acid in proportion of 1 to 20, forty minutes or less before use.

with cotton applicators, wetting the dural surface thoroughly two or three times during this interval; dependent portions, or unusually thick regions of dura should be given extra applications. With care, there will be negligible spillage, readily controlled with small packs and suction, and extensive areas can be treated simultaneously. The wound is then flushed with saline and the scalp closed by interrupted and running vertical mattress sutures of No. 4-0 silk. We prefer not to bury suture material in the infant's scalp, but leave the mattress sutures in place for eight days before removal. Bloody fluid re-

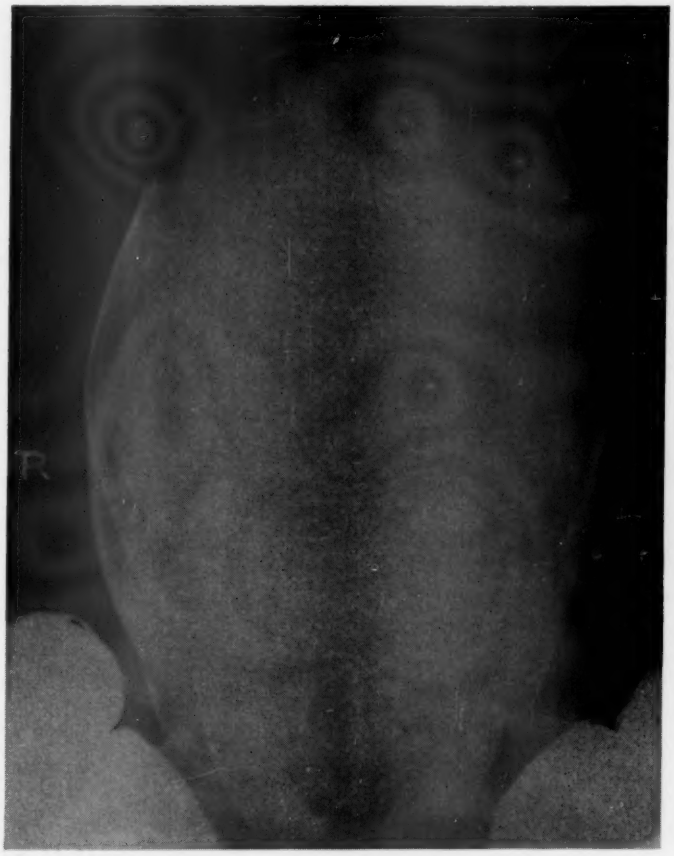

Fig. 5.—Sagittal synostosis in 7-month-old infant treated adequately with 7 per cent iodine on the left dura; polyethylene film used on right. This roentgenogram, six months later, shows new bone growth on right but clear channels parallel to this; left craniectomy has widened and remained open, and this side of cranium is slightly more capacious than right.

quiring aspiration collects beneath the scalp in about half of these patients, as obtains with other craniectomy operations. There have been no adverse local reactions, no interference with wound healing, and no wound infections. Transfusion of 250 to 500 c.c. blood is routinely given during surgery.

Besides the polyethylene film technique and topical drug method described above, we have experimented in a few cases with other means of delaying new bone formation. Ten per cent formalin failed to retard regrowth in one case, and desiccating the dural surface with electrocautery was discarded as undesirable because of possible injury to the cerebral cortex. Resecting the external layer of dura has proved tedious and impractical in a

few attempts. Tantalum foil has not been used in this series. It is of course possible that any of a number of destructive solutions would prove superior to Zenker's-acetic or tincture of iodine for the purpose at hand, and we are attempting to clarify this question by means of animal experimentation as well

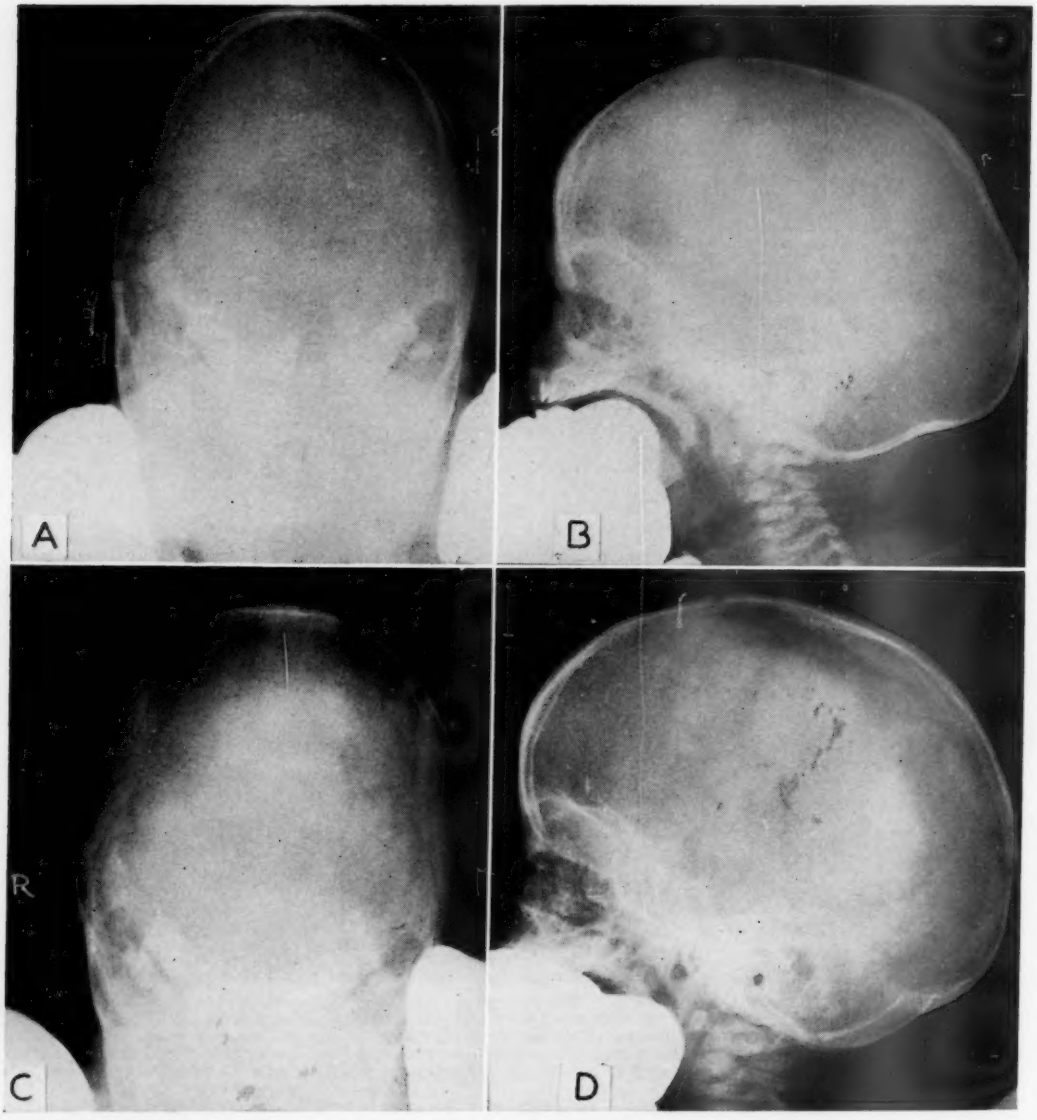

Fig. 6.—*A* and *B*, Anteroposterior and lateral skull roentgenograms of a 4-month-old infant with sagittal synostosis, showing characteristic narrowing and elongation of cranium, fusion and thickening of sagittal suture region. *C* and *D*, Six months postoperatively. Seven per cent iodine used on right craniectomy, polyethylene film on left. Both are functional and head contours have improved considerably, but bone regeneration is more rapid than shown in Fig. 4, *B*. Craniectomies performed in this comparative manner have maintained roentgen appearance of approximately equal functional status for two years. When iodine and Zenker's-acetic solutions are similarly compared, channels treated with the latter preparation usually close more slowly, and are probably superior on functional grounds.

as clinical trial. Considerable investigation will be required before final conclusions are permissible.

A theoretical disadvantage of applying any caustic liquid to the dura mater is the possibility the solution will penetrate this membrane, causing

injury to the cerebral cortex. We have not found evidence that this occurs with iodine forte or Zenker's-acetic solution. These have been placed onto a small area of dura mater in patients undergoing craniotomy for various reasons and specimens of dura later obtained; grossly, the inner dural surface appears smooth and unchanged, the outer surface slightly scarred. Microscopically, there is disorganization of architecture in the external dural layer, and no evidence that the solution has injured or penetrated the inner layer. In a series of dogs now undergoing investigation no dural penetration or cortical injury has been demonstrated.

Obviously, no destructive substance should be used on the dura if this membrane has been perforated or torn. When such an accident occurs in the course of craniectomy operation, the surgeon should suture the laceration and affix polyethylene film to the bone margins rather than risk injury to the cerebral cortex by application of a fixative to the dura.

In considering the choice of methods for craniectomy, reference should be made to the experimental findings of Oppenheimer and associates,[13, 14] and Bering and associates,[1] whose work indicated that implanted pure polyethylene as well as other plastics are capable of producing sarcomas in lower animals. While other investigators[15] have thus far been unable to confirm these results, and it is not known that these substances are carcinogenic in man, this possibility exists and makes one a bit hesitant to employ such materials if a satisfactory substitute is available. Aside from this tentative objection, combination of the chemical method with polyethylene film (or tantalum foil) technique might be considered when it is particularly desirable to delay bone regrowth, as in a young, previously craniectomized patient showing unusually rapid bone regeneration. Another situation with similar indications is that of a newborn infant with advanced craniosynostosis, especially if premature closure involves all of the cranial sutures (oxycephaly). In such a patient, craniectomy should be done within the first month of life and it would be desirable to maintain functional openings for at least three years to avoid reoperation. Although a combined chemical and film procedure might not inhibit bone regeneration enough to attain this objective, it should lengthen the effective period of the initial surgery, delaying secondary operation.

TABLE I. CASE MATERIAL

Total patients operated upon for craniosynostosis	68
Total treated with regrowth-delaying techniques (polythene film, topical iodine, Zenker's-acetic, etc.)	56
Number of latter cases followed more than 6 months	49

TABLE II. INCIDENCE OF SUTURES PREMATURELY SYNOSTOSED (SURGICAL PATIENTS)

Sagittal	47
Sagittal and lambdoid	2
Sagittal and coronal	1
Sagittal and squamosal	2
All (oxycephaly)	7
Metopic	1
Coronal	8
Total	68

It is not the purpose of this paper to contend that chemical treatment of the dura is superior to any other method for delaying regrowth of bone after craniectomy. This technique is submitted as an alternate approach which may offer advantages because of its apparent efficacy, relative ease of application, and freedom from risk.

CONCLUSIONS

1. A technique is presented for delaying bone regrowth and fusion of craniectomies performed for treatment of premature suture closure (craniosynostosis) in infants and young children.

2. This method consists of thorough application of Zenker's-acetic fixative or 7 per cent tincture of iodine (Strong Iodine tincture, N.F.) on the surgically exposed dura mater to reduce osteoblastic properties of its external layer. Zenker's solution appears to be more effective, and is recommended in preference to iodine.

3. Results in 30 cases with sufficient follow-up compare favorably with those obtained by the polyethylene film technique, indicating that functional channels are maintained for two years or more after operation.

4. It is again advised that operation for craniosynostosis be performed before the age of 6 months to prevent complications caused by restriction of brain growth. Simple craniectomies are inadequate for this purpose and must be augmented by a fusion-inhibiting process, to prolong beneficial effects of operation and provide best cosmetic results.

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Editorials

Dysphagia

Dysphagia is defined in medical dictionaries as difficulty in swallowing. It is pertinent to point out, however, that dysphagia is a very broad term and that the difficulties in swallowing resulting from such various causes as carcinoma of the esophagus, esophageal diverticulum, esophageal stricture, and myasthenia gravis are really quite different one from another. This can be tested readily by the simple expedient of watching patients with dysphagia due to various causes drink a glass of water.

However dysphagia manifests itself, it is an extremely important symptom and indicates disturbance of a very vital function; hence it deserves early and thorough investigation whenever it occurs. Dysphagia should be investigated promptly because it is really a rather late manifestation of disease in most instances even though it is the first and most outstanding symptom common to disorders of the esophagus. The elasticity of the esophagus is so great and its function so efficient that a diverticulum must reach considerable size, a carcinoma must extend to involve most of the circumference of the esophagus, and cardiospasm and stricture must have been present for some time before dysphagia develops. Once dysphagia has developed, its cause can be determined in most instances by means that are readily available to physicians everywhere. Roentgenologic, endoscopic, and motility studies provide prompt and accurate diagnosis of most esophageal disorders.

Since difficulty in swallowing can hardly be ignored by even the most phlegmatic or careless person, it is disturbing to realize that, even in this supposedly enlightened age, a patient so afflicted rarely receives surgical attention until he has had the symptom for months or even years. When, in addition, it is recalled that dysphagia is a rather late manifestation of disease in the first place, it is evident that the interval between the onset of the causative disease and the surgical treatment of that disease is excessively long. Particularly significant is the fact that often much of this loss of time occurs after the patient has consulted his physician regarding his dysphagia. Practically every reported experience with carcinoma of the esophagus mentions or emphasizes that the average duration of dysphagia before diagnosis and treatment was six months or more. Patients with diverticulum of the esophagus, cardiospasm, or esophageal stricture usually give a history of having had dysphagia for years before appropriate diagnosis and treatment. With available diagnostic procedures it is possible to diagnose carcinoma and other diseases of the esophagus even before they produce dysphagia. Unfortunately, it is not feasible to do the necessary diagnostic tests as screening procedures. However, failure to investigate promptly any complaint of dysphagia seems unexcusable.

Considerable pessimism has been expressed about the results of surgical treatment of carcinoma of the esophagus. Such pessimism is at least partially justified when one considers the advanced lesions that surgeons are called upon to deal with. Furthermore, it is unlikely that surgeons can extend their surgical procedures further, lower the risk of operation, or improve the results now obtainable if they continue to have an opportunity to see and treat only patients with far-advanced carcinoma of the esophagus. However, there is no question that if carcinoma of this organ could be diagnosed and treated earlier it could be treated effectively.

There is little excuse for letting a patient with dysphagia due to cardiospasm go on with the condition undiagnosed and untreated until the esophagus becomes a dilated, tortuous, thick-walled sac, when a simple cardiomyotomy or Heller operation on the esophagogastric junction early in the development of the lesion could bring relief.

A patient with dysphagia due to pharyngoesophageal diverticulum should not be neglected until he becomes malnourished, a social outcast because of his bad breath, or a pulmonary cripple because of aspiration of material from the diverticulum into his tracheobronchial tree, when surgical excision of the diverticulum could have relieved him of his difficulties. Nor should reflux esophagitis due to a sliding esophageal hiatal hernia be allowed to produce permanent shortening and stricture of the esophagus because of failure to recognize and repair the hernia before irreversible changes in the esophagus have occurred.

The esophagus is a remarkable organ. It functions with amazing efficiency considering the burdens imposed upon it. However, it is frequently the site of development of serious disease. The symptom common to most diseases of the esophagus is dysphagia. Unfortunately, this symptom is a relatively late manifestation of esophageal disease in many cases. Because dysphagia does not develop early, it becomes even more essential that it be investigated promptly when it does occur. The cause of dysphagia can be determined easily and promptly in most instances. Most of the causes can be treated by surgical means, but earlier diagnosis is essential to safer and more effective surgical treatment. Early diagnosis of diseases of the esophagus is possible if patients and physicians will give dysphagia the attention it deserves.

—O. Theron Clagett.

Permanent Diversion of the Urine

Permanent diversion of the urine above the bladder has such serious implications for the patient that it is done only if more conservative methods are not applicable to conditions which threaten life or make it intolerable. There are three fairly clear reasons for its use: neoplastic disease necessitating removal of the bladder or urethra; a bladder incapable of holding enough urine to permit comfortable life; and ureters unable to propel urine efficiently past the resistance of their intramural portions. The last is experimental.

The indications for removal of the bladder need not be detailed here, but possible causes for abandoning it with or without removal require discussion. Reasons include exstrophy, the neurogenic dysfunction of severe meningomyelocele, and the seriously contracted bladder of interstitial cystitis or of posttuberculous fibrosis, especially when the thickened vesical wall causes ureteral stenosis or reflux. Similarly, an occasional vesicovaginal or intestinovesical fistula may be irreparable because of fibrosis from previous operations or irradiation, or because of the presence of neoplastic tissue. One may be driven to consider urinary diversion in urinary incontinence due to postoperative fibrosis of the urethral sphincters, and it is possible that it may be useful for some of the disturbances of urination following severe injuries of the spinal cord.

The statement that inability of the ureters to propel the urine efficiently into the bladder may require urinary diversion raises interesting questions. Every urologist knows that congenital bilateral ureterectasis may cause progressive hydronephrosis which cannot be arrested nor improved by local measures, and which finally leads to death from renal insufficiency. Similar difficulties may arise from ureteral reflux, and in children in whom correction of an advanced obstruction of the vesical neck fails to halt the progress of hydronephrosis and pyelonephritis. In such cases the ureters have become so thin, dilated, and tortuous that peristalsis is ineffective. Straightening and reimplanting of such ureters is usually of transitory benefit, and the thinness of the ureteral wall makes inapplicable Hutch's operation for prevention of reflux. Whether such ureters will be efficient enough to preserve remaining renal tissue if anastomosed to an isolated ileal loop, with its resultant complete removal of all obstacles to the passage of urine, remains to be seen. Some of these problems may be solved, if the bladder is efficient, by replacing useless ureters with ileal segments.

There are several standard methods of permanent diversion of the urine. The simplest, and, in terms of surgical risk alone, the safest are nephrostomy and cutaneous ureterostomy. Since both ordinarily require inlying catheters, infection, particularly with urea splitters, is inevitable. The frequency with which pyelonephritis and lithiasis follow these operations when patients survive for long periods contraindicates their use except as temporary expedients or as palliative procedures when long survival cannot be anticipated. Occasionally, if the ureters are thick walled and dilated, one can make a cutaneous ureterostomy so that the protruding ends of the ureters are surrounded by skin tubes. The patient can then wear ureterostomy cups instead of catheters, thus preventing the continuous contamination of the kidneys which comes from catheters. Unfortunately, when this is done with normal or thin-walled ureters, retraction of the skin tubes and stricture of the cut ends of the ureters usually result.

Ureterosigmoidostomy has been a popular method of permanent diversion of the urine but has serious disadvantages. Too often it leads to stenosis of the terminal ureters either at their cut ends or in the intestinal wall. Moreover, unless the anastomosis is both properly made *and* heals kindly, the high pres-

sures prevailing in the colon, particularly during defecation, may drive intestinal contents into the kidneys. These factors combine to damage the kidneys after a high proportion of these operations. The importance of renal disease in aggravating hyperchloremic acidosis from absorption of urinary chlorides and other acid radicals by the colon is well understood (Ferris and Odel, Lapides, Creevy).

The severity of this damage may be minimized in several ways. Opportunities for reflux are reduced and sometimes eliminated by combining the terminolateral mucosa-to-mucosa anastomosis of Nesbit with Coffey's submuscular tunnel (Leadbetter). Matters can be further improved by making a diverting colostomy above the site of implantation, as suggested by Mauclaire, in 1895, and by many others since. It has never become popular, presumably because of the inconveniences of colostomy. Reluctance to perform colostomy here is doubtless due to the fact that the renal complications of ureterosigmoidostomy disable and finally kill the patient much more slowly than does cancer of the rectum for which colostomy is a standard procedure. The danger in the former instance is emphasized by the pronounced reduction in longevity observed by Harvard and Thompson after ureterocolostomy for exstrophy of the bladder in a series of 98 cases followed for five to thirty-five years.

The number of cases treated by ureterointestinal anastomosis with a diverting colostomy is too small to permit comparison of results, but logic favors this combination, especially since Smith and Hinman, Jr., have demonstrated a striking reduction in pressures prevailing in the rectum after colostomy.

Attempts to procure the advantages of colostomy without its attendant incontinence of gas and feces probably began in 1898 when Gersuny proposed to implant the ureters into a blind rectal pouch and to draw the divided sigmoid through the anal sphincter beside the rectum. Others have since advocated this method, and Lowsley has recently revived it. While it obviously cannot provide as clean a reservoir for the urine as if the colostomy were at a distance from the anus, it seems to deserve further trial.

"Wet colostomy" is less likely to injure the kidneys than is conventional ureterosigmoidostomy because the lack of a sphincter lowers intraluminal pressures, thus reducing the opportunities for reflux; the bowel serves as a conduit rather than as a reservoir, and so cuts chances of absorption. However, the fact that it exposes the kidneys to the fecal stream is objectionable.

To avoid these handicaps, Bricker anastomoses the ureters to an isolated loop of ileum, one end of which is closed while the other emerges like an ileostomy. The operation is more extensive and time-consuming than ureterosigmoidostomy with colostomy and, because of the additional intestinal anastomosis involved, carries more danger of fistulas and intestinal obstruction (Cordonnier), and an apparatus must be worn to collect the urine. Advantages include a urinary channel uncontaminated by feces; the short loop without a sphincter minimizes opportunities for reflux and absorption; and it requires no foreign body in the urinary tract. It appears at present to be the best

method so far devised when the anal sphincter is incompetent or absent, and its usefulness for complete diversion of the urine while the bladder is being repaired or reconstructed has not yet been explored. It will require some time to compare its effects upon the upper urinary tract with those of other methods because it has been employed mainly for malignant lesions which offer poor prospects for long survival.

The "ileocecal bladder" of Gilchrist and Merricks, utilizing the ileocecal valve to prevent urinary leakage between catheterizations, requires an extensive operation with the same risks as that of Bricker but lacks its chief advantage: the absence of a foreign body within the urinary channel. Since it is known that long-continued catheterization causes infection, it is hard to see why it should be any safer with an artificial than with a normal bladder. Because the cecum and ascending colon can absorb electrolytes, it seems likely that the occurrence of pyelonephritis in long-time survivors will lead to hyperchloremic acidosis.

Artificial bladders made from segments of colon and anastomosed to the urethra and ureters have succeeded in the dog (Rubin, Scott) but apparently have not been applied to man.* Couvelaire used in this manner a loop of ileum with a capacity of 150 c.c., and the patient survived. It seems unlikely that larger ileal bladders are practical because of the absorptive capacity of the ileum. Grotzinger, Shoemaker, and associates have been able to replace most of the dog's bladder with an ileal graft with its serosa exposed to the urine; it becomes lined with transitional epithelium (urothelium) which resists absorption of vesical contents. It remains to be seen whether an urethral stump can supply enough urothelium to line a whole bladder made in this fashion.

Considering these rather fragmentary data, one must conclude that a wholly satisfactory means of diverting the urine permanently without injuring the kidneys nor subjecting the patient to serious inconvenience has yet to be devised and applied with safety mainly because we lack the means to control infection for indefinite periods. The technical methods are at hand if someone succeeds in producing a universally effective, nontoxic antibiotic to which bacterial resistance cannot develop. Unfortunately, this is still a dream.

—*C. D. Creevy.*

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE VITAMIN B_{12} DEFICIENCY STATE ENGENDERED BY TOTAL GASTRECTOMY

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INTRODUCTION

IN THE last century and the early part of this one, the simultaneous occurrence of atrophy of the mucosal lining of the stomach and Addisonian pernicious anemia was recognized by several observers,[13, 15, 25] but the causal relationship was never understood. It is not surprising that on the very rare occasion when total gastrectomy was performed, there should be interest in the blood picture following the surgical procedure. Lord Moynihan[37] in 1911 reported that a woman upon whom he had performed a total gastrectomy three years previously for carcinoma died with weakness, breathlessness, pallor, and evidence of profound anemia. At autopsy there was widespread lack of bone marrow and absolutely no evidence of carcinoma, local or metastatic. In the following twenty years there were three other patients reported who had undergone total gastrectomy and had developed, at varying times after this procedure, an anemia suggestively Addisonian in type.[12, 22, 52]

In previous years great emphasis has been placed upon the blood changes. That the blood cells are not the only body cells affected in Addisonian pernicious anemia is now perfectly clear. Changes in the cells of the posterior and lateral columns of the spinal cord have been known for many years.[46] More recently Graham and Rheault[18] have shown that cells scraped from the buccal and gastric mucosa exhibit macrocytosis.

The macrocytosis of cells seen in this clinical state is thought to be a result of a defect in the synthesis of nucleoprotein resulting from a bodily deficiency in some substance necessary for this process.[9] This substance is now thought to be vitamin B_{12}. The deficiency causes a slowing of cellular division with a decrease in the total number of cells produced, but with a concomitant increase in the individual size of those cells which are produced. Presumably all cells of the body are affected.

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Although vitamin B_{12} has been identified only recently, its existence had been suggested by Castle[8] in 1929. He postulated that two substances were needed by the body for normal maturation of erythrocytes.

The one substance (extrinsic factor), now thought to be vitamin B_{12}, he suggested was contained in ingested food. The other substance (intrinsic factor) was thought to be secreted into the gastrointestinal tract by gastric mucosal cells. Castle suggested that an absence of either one inhibited the normal maturation of red cells, and that macrocytosis of the erythrocytes, reduction in their total number, and the presence of the megaloblasts in the marrow were all manifestations of this inhibition of normal maturation.

Unlike vitamin B_{12} (the extrinsic factor), the intrinsic factor has not been identified chemically. However, a great deal regarding its physiological activity is known.[9] It is now clear that its function is only to enhance the intestinal absorption of vitamin B_{12}. It is not necessary for any direct effect upon the cells for their nuclear metabolism. Adequate parenteral administration of vitamin B_{12} alone will correct the deficiency state completely.

Total gastrectomy was an exceedingly rare operation prior to 1930. Finney and Reinhoff[14] reported a total of 67 undoubted cases and a possible 116 cases reported in the world's literature to 1930. Wintrobe[54] in 1951 recognized only 12 cases of pernicious anemia as having developed in 46 patients with total gastrectomies who survived three years or longer as reported in the world's literature.

In addition, hematological data obtained at about this time in the experimental animals subjected to total gastrectomy tended to confirm the idea that pernicious anemia was a rare occurrence after the operation. In 1932, Mann and Graham[34] reported that 6 dogs subjected to total gastrectomy, and surviving from two to six years after the operation, did not become anemic as measured by red cell count and hemoglobin determination. However, no smears of the peripheral blood were made. In 1933, Ivy, Morgan, and Farrell[27] reported that in 14 dogs subjected to total gastrectomy, no cases of primary anemia developed. One dog was followed for six years, one for five years, 3 for two years, and 2 for six months. In 1935, Shumaker and Wintrobe[48] subjected 19 dogs to total gastrectomy. Seven survived the operation and were observed for one year. Six developed a slight secondary anemia in one month after operation. Their stools contained blood as measured by the guaiac reaction. Two dogs when poisoned with carbon tetrachloride developed a severe macrocytic anemia shortly before death. In 1939, Bussabarger, Ivy, Wigodsky, and Gunn[6] reported that, in 8 monkeys subjected to total gastrectomy, 5 who lived as long as two and one-half years did not develop pernicious anemia. One monkey, however, at eighteen months after operation showed macrocytosis of the erythrocytes on smear of the peripheral blood. In 1940, Ivy[26] in reporting on his series of observations in experimental animals subjected to total gastrectomy wrote, "It cannot be stated that total gastrectomy causes pernicious anemia, combined degeneration of the spinal cord, stomatitis and glossitis, in the rat (6 mos.–1 year), in the dog (1–12 years), pig (1–3 years), or monkey (1–2.6 years)."

On the other hand, in 1936 Bence[4] reported that in pigs subjected to total gastrectomy an iron deficiency anemia developed early, and later a macrocytic type of anemia developed. Bone marrow studies showed changes suggestive but not pathognomonic of pernicious anemia. In 1940, Geiger, Goodman, and Claiborn[16] showed clearly that the antianemic potency of the liver of hogs subjected to total gastrectomy decreased significantly by the second month postoperatively and was completely depleted by the sixth month postoperatively. In 1941, Petri, Bing, Nielsen, and Nielsen[40] reported independently the same observation made by Geiger, Goodman, and Claiborn. In 1943, Petri, Norgaard, Trautner, and Kiaer[41] reported that in 14 pigs subjected to total gastrectomy within one year an undescribed type of anemia developed as well as central nervous system changes suggesting subacute combined degeneration. This was interpreted by them as a manifestation of nicotinic acid deficiency.

In 1947, Longmire[31] presented a large series of patients subjected to total gastrectomy. Since that time several other reports of series of patients subjected to total gastrectomy have appeared by Smithwick,[49] Kelley, MacLean, Perry, and Wangensteen,[28] and Scott and Longmire.[47] In 1947, MacDonald, Ingelfinger and Belding[32] in studying the late effects of total gastrectomy reported that two patients surviving two and five years, respectively, after the operation developed a macrocytic, hyperchromic anemia. No bone marrow studies were done. In 1953, Blake and Rechnitzer[5] stated that of ten patients subjected to total gastrectomy, six had developed macrocytosis of the erythrocytes within three years of operation, and four of these patients had megaloblasts develop in the marrow, one at 2¼ years after operation, another at 2¾ years, another at 3 years, and another at 7 years. Since 1950, other communications have appeared in the literature reporting cases of macrocytic megaloblastic anemia developing after total gastrectomy.[11, 19, 39]

Despite all of these, there is still confusion in the understanding of the vitamin B_{12} deficiency state engendered by total gastrectomy, and in its pathogenesis. The present communication describes the vitamin B_{12} deficiency state which occurs in the human being when the stomach is removed. This deficiency state has been studied in collaboration with Dr. Moses Paulson in 28 patients subjected to total gastrectomy in The Johns Hopkins Hospital between the years 1944 to 1956, and in 2 other patients operated upon elsewhere, but referred for study. The majority of operations at this hospital were performed by Dr. William Longmire[31, 47] and Dr. H. W. Scott.[47]

OBSERVATIONS

Twenty-eight patients subjected to total gastrectomy at The Johns Hopkins Hospital and one patient operated on at the Baltimore City Hospital have been followed carefully preoperatively and postoperatively for various periods of time up to twelve years (Table I). Another patient, who, on maving to Baltimore, was referred to our hospital by Dr. Sanford Marshall of Boston seven years after a total gastrectomy, has been followed here for ten years. Gastric analyses were done preoperatively on 25 patients. Eleven individuals showed free acid, and 18 showed acid after stimulation with histamine. Careful

TABLE I. TOTALLY GASTRECTOMIZED PATIENTS

CASE NO.	J. H. H. HIST. NO.	AGE	SEX	TIME FROM OPERATION TO		GASTRIC LESION	GASTRIC ANALYSIS		TIME IN YEARS TO DEVELOP:			CLINICAL FEATURES					
				DEATH	PRESENT (YR.)		FREE ACID°	TOTAL ACID°	MACRO.	ANEMIA	MEGAL'S	PALLOR	LEMON-YELLOW SKIN	GI COMPLAINTS	NEUROLOGICAL LESION	TREATMENT	RESPONSE
1.	403827 S. D.	48	M	2 mo.		Ca.	0	10	0	0	*	0	0	0	0	0	
2.	505984 L. W.	60	M	5 mo.		Ca.	0	0	½	0	*	0	0	0	0	0	
3.	358539 J. S.	47	M	5 mo.		Ca.	Not done		0	0	*	+	0	0	0	0	
4.	358706 F. B.	49	M	6 mo.		Ca.	0	18	¼	0	*	0	0	0	0	0	
5.	412039 R. E.	53	M	1 yr.		Ca.	29	75	½	0	*	+	0	0	0	0	
6.	432881 J. M.	46	M	1		Ca.	18	24	½	0	None	+	0	0	0	0	
7.	465384 M. H.	53	F	1½		Lympho-sarcoma	0	0	½	0	*	0	0	0	0	0	
8.	134386 S. T.	46	F	1½		Ca.	10	20	1	1	*	+	0	+	0	0	
9.	343226 D. B.	49	M	1½		Ca.	0	0	1	1	None	+	0	+	0	0	
10.	508875 L. H.	60	M	1½		Ca.	10	10	1	1	None	+	0	0	0	0	
11.	484491 J. C.	64	M	2		Ca.	0	0	1	0	None	+	0	0	0	0	
12.	365976 J. B.	41	M	2		Ca.	0	26	1½	0	*	0	0	0	0	0	
13.	367072 G. L.	47	M	2		Ca.	0	14	½	–	*	0	0	0	0	0	
14.	250931 F. J.	63	M	2		Ca.	0	0	1½	–	None	+	0	+	0	0	

15.	659382 G. S.	70	M		2½	Ca.	Not done		1	1	1½	+	0	+	0	Vit. B_{12} I. M.	Good HCT. 21 → 37 MCV 144 → 90
16.	423074 N. S.	50	M	3		Ca.	Not done		2	2½	None	+	0	0	0	0	
17.	183335 G. G.	63	M		3	Ca.	Not done		1	2	2½	+	+	0	+	Vit. B_{12} I. M.	Good HCT. 30 → 41 MCV 106 → 80
18.	327801 N. M.	67	F	3½		Ca.	Not done		1	2	None	+	0	0	0	0	
19.	493788 D. Y.	59	M	3½		Ca.	4	10	2	3	None	+	0	0	0	0	
20.	566008 N. V.	62	M		5	Neuro-fibroma	50	80	3	4	None found	0	0	+	0	Vit. B_{12} I. M.	Good HCT. 27 → 40 MCV 106 → 80
21.	413731 H. F.	58	F	5¼		Ca.	20	68	2	2½	3	+	0	+	0	Vit. B_{12} I. M.	Good HCT. 22 → 38 MCV 120 → 80
22.	445863 R. W.	58	M	6		Ca.	0	0	3	3½	4	0	0	0	0	Failed to follow suggested R	
23.	287808 J. C.	69	M	7		Benign ulcer	14	45	4½	5	5	+	+	+	+	Vit. B_{12} I. M.	Good HCT. 30 → 40 MCV 119 → 82
24.	462465 H. D.	59	M		8	Chronic gastritis	5	15	1½	2	2½	+	0	+	0	Vit. B_{12} I. M.	Good HCT. 30 → 40 MCV 98 → 83
25.	441562 W. C.	59	M		8	Lympho-sarcoma	0	0	1	3	7	+	+	+	+	Vit. B_{12} I. M.	Good HCT. 22 → 33 MCV 110 → 88 CNS lesion cured

TABLE I—CONT'D

CASE NO.	J. H. H. HIST. NO.	AGE	SEX	TIME FROM OPERATION TO		GASTRIC LESION	GASTRIC ANALYSIS		TIME IN YEARS TO DEVELOP:			CLINICAL FEATURES				TREATMENT	RESPONSE
				DEATH	PRESENT (YR.)		FREE ACID°	TOTAL ACID°	MACRO.	ANEMIA	MEGAL'S	PALLOR	LEMON-YELLOW SKIN	GI COMPLAINTS	NEUROLOGICAL LESION		
26.	153979 E. W.	52	F		8	Ca.	20	38	5	6	None	0	0	0	+	Vit. B_{12} I. M.	Good HCT. 38 → 44 MCV 95 → 88 CNS lesion cured
27.	415404 J. W.	47	M		9	Ca.	0	25	6	6½	8	+	+	+	+	Vit. B_{12} I. M.	Good HCT. 11 → 41 MCV 105 → 83 CNS lesion cured
28.	338511 J. P.	65	M		12	Ca.	42	66	6	8	11	+	0	+	0	Vit. B_{12} I. M.	Good HCT. 34 → 40 MCV 99 → 82
29.	326706 J. W.	63	M		12	Ca.	0	18	4	5½	6	0	0	0	0	Vit. B_{12} I. M.	Good HCT. 30 → 42 MCV 100 → 80
30.	375636 M. G.	57	F		17	Lympho-sarcoma	0	30	7	7	*	+	0	+	+	Liver extract I. M. later Vit. B_{12} I. M.	Good HCT. 20 → 40 MCV 139 → 90

*Bone marrow not examined.

physical examinations including neurological examination were made at regular intervals. Frequent examinations of the peripheral blood were done and examinations of bone marrow aspirations were made at approximately six-month intervals. Treatment with liver extracts or with vitamin B_{12} was purposefully withheld, consistent with safety to the patient, in order to observe the development and natural course of this surgically created vitamin B_{12} deficiency state.

There were 24 male and 6 female patients subjected to this operation. At the time of operation, 2 males and 2 females were between 30 and 39 years of age, 9 males and 1 female were between 40 and 49 years of age, 8 males and 2 females were between 50 and 59 years of age, and 5 males and 1 female were between 60 and 69 years of age. All were operated on for presumed diagnosis of gastric carcinoma. The anatomical diagnoses from the gross and microscopic examination of the resected stomach are listed in Table II.

TABLE II. PATHOLOGIC DIAGNOSES—RESECTED STOMACHS

Carcinoma	24
Lymphosarcoma	3
Benign ulcer	1
Neurofibroma	1
Syphilitic gastritis	1

Twenty-six of the patients have survived one year or longer following operation, 11 five years or longer, and 3 ten years or longer. The longest survival period has been seventeen years. Ten patients remain alive at the time of this writing, 1 patient two and one-half years after operation, 1 three years, 1 five years, 3 eight years, 1 nine years, 2 twelve years, and 1 seventeen years. Thus, there has been an adequate period of time to observe the natural consequences of total gastrectomy.

The first evidence of vitamin B_{12} deficiency to appear is macrocytosis of the erythrocyte. This occurred within six months to seven years after operation with the average time of development two and one-half years after operation. Next to appear was anemia. The patient was considered to be anemic when the hematocrit was 37 per cent or less.[39] This occurred anywhere from six months to nine years after operation, with the average time of development four years after operation. Usually by the time the fall in hematocrit was first detected, the individual exhibited pallor and complained of some weakness and easy fatigability, as well as soreness of the tongue. The latter symptoms are difficult to evaluate, for individuals subjected to total gastrectomy have, as Paulson[38] has pointed out, numerous symptoms related to the gastrointestinal tract including eructation, heartburn, epigastric fullness, "dumping," difficulty with bowels, fatigability, and weakness. These develop early after operation and are related to altered mechanical factors and changes in metabolism of carbohydrates resulting from the gastrectomy. Invariably after anemia was first detected in a patient, megaloblasts were found in the bone marrow within one year. The time of development in individual cases varied from two years to ten years with an average of four and one-half years. The development of these changes is shown in Table III.

TABLE III. DEVELOPMENT OF MACROCYTIC MEGALOBLASTIC ANEMIA AFTER TOTAL GASTRECTOMY

OBSERVED CHANGE	TIME IN YEARS		
	MIN.	MAX.	AV.
1. Macrocytosis RBC MCV> 94	½	7	2½
2. Anemia HCT.< 37	½	9	4
3. Megaloblastic marrow	2	10	4½

Three of the patients exhibited combined nervous system disease which developed six, seven, and eight years, respectively, after operation. These individuals had macrocytosis, anemia, and megaloblastic bone marrow. They had been under close observation but failed to return for one to two years despite urging onthe part of families and physicians. In this interim, neurological complications appeared, and these symptoms caused the patients to return for aid.

In four patients the absorption of vitamin B_{12} in the intestine was studied by Krevans and associates,[30] in 1 patient one year after operation, in 2 patients three years after operation, and in still another four years after operation. In these patients a single oral dose of vitamin B_{12} (0.5 mcg.) labeled with cobalt^{60} was administered. The radioactivity recovered in the feces was measured. The percentages of recovery of radioactivity are shown in Table IV.

TABLE IV. VITAMIN B_{12} INTESTINAL ABSORPTION STUDIES

(Per cent radioactivity recovered in stools after single oral dose [0.5 mcg.] cobalt^{60}-labeled vitamin B_{12}.)

PATIENT	PER CENT RECOVERED
Normal	10-49
G. S.	70
H. D.	87
N. V.	90
W. C.	92

In the patients who developed the full hematological picture of vitamin B_{12} deficiency (macrocytosis, anemia, and megaloblastic bone marrow), treatment with liver or vitamin B_{12} was instituted. Table I also shows the results of this treatment. Response is measured by decrease in mean corpuscular volume, rise in hematocrit, and disappearance of megaloblasts from the marrow. Forty-five micrograms of vitamin B_{12} was given intramuscularly every week for eight weeks when treatment was instituted. Then the patients were put on maintenance doses of 45 mcg. intramuscularly every month.

Subjectively the individuals responded well with disappearance of soreness of tongue, increase in sense of well-being, and loss of weakness and easy fatigability. Two showed a change in their emotional reactions. Crankiness and waspishness gave way to patience and joviality.

The three patients with combined nervous system disease recovered after treatment was instituted. The paresthesias disappeared and motor power improved. Ataxia, which was present in one individual, disappeared.

COMMENT

From the observation on the patients reported in this communication, it appears clear that vitamin B_{12} deficiency is inevitable after total gastrectomy

if the patient lives long enough. Time is a factor, for this deficiency requires from two to ten years to appear. Early manifestations of the deficiency (macrocytosis of the erythrocytes, glossitis) can be clearly recognized before more serious manifestations (anemia, megaloblastic marrow, central nervous system changes) occur.

In Addisonian pernicious anemia the gastric mucosal change either abolishes the secretion of intrinsic factor or so reduces the total amount secreted that there is too little intestinal absorption of the ingested vitamin B_{12} to provide adequate amounts of the vitamin for normal cellular metabolism.

Studies to demonstrate the absorption of vitamin B_{12} labeled with radioactive cobalt (measuring fecal excretion of the radioactivity) have shown that between 60 and 80 per cent of a single oral dose of 0.5 mcg. of vitamin B_{12} is absorbed by the normal individual. In the patient with Addisonian pernicious anemia, only 20 per cent or less of such an oral dose is absorbed.[23] Giving desiccated hog stomach or normal human gastric juice concurrently or within one-half hour of administration of the dose of labeled vitamin, however, will enhance the absorption so that it will be between 60 and 80 per cent.[20, 33]

Since vitamin B_{12} must be taken in the food, absorbed by the intestinal mucosal cells, with the aid of some substance secreted in the gastric juice, and transported to all the cells of the body, it is conceivable that a deficiency state may occur from many diverse causes. Logically one might expect that an individual might have a diet deficient in the vitamin. There might be a deficient amount of intrinsic substance to facilitate intestinal absorption. There might be increased utilization of the vitamin in the intestinal tract by bacteria or parasites, reducing thereby sufficient amounts available for absorption. There might be changes in the intestinal mucosal cells preventing the transport of the vitamin across the intestinal wall. Finally, there might be some defect in the transport mechanism for vitamin B_{12} in the body, preventing the vitamin from reaching the end organ, the cell.

In truth, all of the above causes save one have been clearly shown to exist in the human being and to be associated with a vitamin B_{12} deficiency state. Wokes, Baden, and Sinclair[55] reported recently from England that some members of a religious sect who abstain from all meat, dairy products, and sea food have developed a vitamin B_{12} deficiency state after five years or so on their diets of vegetables only. Spontaneous atrophy of the gastric mucosa and associated hematological changes have been known for 100 years. Atrophy of the gastric mucosa in association with ingestion of lye or other corrosive agents or in association with syphilis of the stomach (linitis plastica) and followed by the development of macrocytic, megaloblastic anemia has been reported.[1, 11, 44] This communication has pointed out that removal of the stomach surgically results in removal of the cells secreting intrinsic factor and is followed by vitamin B_{12} deficiency. Increasing utilization of vitamin B_{12} by bacteria in blind loops in the intestinal tract has been clearly shown to occur[21, 29] and to be the cause of the pernicious anemia picture which has long been recognized by clinicians, but whose cause was heretofore unknown.[3] Von Bonsdorff[53] has

shown that the pernicious anemia so long recognized as an accompaniment of fish tapeworm infestation results from increased utilization of the vitamin B_{12} by the parasite within the intestinal lumen.

In sprue there are suggestive evidences of vitamin B_{12} deficiency (hematological changes) which could result from the intestinal mucosal cell's failure to absorb vitamin B_{12}, since the diet is generally sufficient and gastric secretion is adequate.[29, 45] Lastly, it has been shown in a single case that there can exist a deficiency in the specific serum protein necessary for the binding and transport of vitamin B_{12} so that a B_{12} deficiency state has been engendered not from deficient diet or deficient intestinal absorption, but rather from lack of transport of the vitamin to all the body cells.[24]

The time factor in the depletion of the body stores of vitamin B_{12} has now been clearly shown in the human patient subjected to total gastrectomy in measurement of serum B_{12} levels. Mollin and Ross[35] first showed that vitamin B_{12} levels in the serum were decreased after total gastrectomy. In two patients one and one-half years and two years after the operation, respectively, both of whom exhibited a macrocytic megaloblastic anemia, the serum levels of vitamin B_{12} were 20 to 40 μmcg./L. in the first patient, and 50 μmcg./L. in the second. The mean normal serum level of vitamin B_{12} as measured by them is 358 μmcg./L. The mean normal serum level in 10 patients with untreated pernicious anemia observed by them was 43 μmcg./L. Pitney and Beard[42] measured the serum levels of vitamin B_{12} at intervals after total gastrectomy in one patient. At eight months following operation, the patient had a level in the low range of normal (100 μmcg./L.). At twenty months, the levels were in the range of those in pernicious anemia (46 μmcg./L). Pitney, Beard, and van Loon,[43] from recent experiments performed on liver hemogenates, suggests that the serum has a greater affinity for vitamin B_{12} than liver, and thus the normal serum level is maintained in the presence of greatly depleted liver stores. Geiger, Goodman and Claiborn's study[16] on the relationship between time and depletion of the antianemic factor in hogs' liver following total gastrectomy fits well this concept of Pitney. Although their hogs' livers were quite depleted, the hogs themselves showed no changes in the peripheral blood or marrow suggestive of a deficiency of the antianemic principle. Serum B_{12} levels were then unknown.

The late appearance in totally gastrectomized patients of symptoms of vitamin B_{12} deficiency and changes in the peripheral blood, as seen in Table III, can well be explained by considering the normal daily requirement of vitamin B_{12} and its total body content. It has been postulated[9] that the body requires about 1 mcg. of vitamin B_{12} per day. Girdwood[17] has estimated from an assay of normal tissues that 1,000 to 2,000 mcg. of vitamin B_{12} may be stored in the body. If 1 mcg. is required per day, and the total body store is the minimum reported by Girdwood, 1,000 mcg., then one could estimate that it would take at least two and one-half years before the stored vitamin B_{12} in the body were totally depleted in face of no replenishment.

In light of these observations, reinterpretation of some of the aforementioned data in the experimental animals is permissible. Some time must elapse

before the body is completely depleted of its stores of vitamin B_{12}. One would judge that the experimental animals who failed to show a pernicious anemia picture were sacrificed before they had been completely depleted. Actually in the reports when smears of the peripheral blood were made, macrocytosis of the erythrocytes was invariably found, but its significance was not then apparent.

In the cases in human beings with gastric cancer subjected to total gastrectomy and not developing pernicious anemia reported before 1950, the survival time was invariably short, some individuals dying postoperatively and others at times up to one year. These patients subjected to the operation were usually poor surgical risks and some had metastatic disease at the time of the operation. At best, survival was short, and thus they did not live long enough for the picture of vitamin B_{12} deficiency to become evident.

This deficiency state can readily be corrected by replacement with vitamin B_{12}. Parenteral administration of vitamin B_{12} has been employed in all of the cases reported here. Although preparations of vitamin B_{12} have been given by the oral route,[10] and by nasal insufflation,[36] parenteral administration is the only route at present to insure adequacy of administration.

That the deficiency of vitamin B_{12} in these patients is caused by lack of intestinal absorption of the vitamin as a consequence of the loss of the source of intrinsic factor is shown clearly by the absorption studies with cobalt^{60}-labeled vitamin B_{12} in the four patients reported in this communication. Swendseid and associates[51] were the first to demonstrate the vitamin B_{12} absorption defect in patients with total gastrectomy by means of this technique. Later, in patients with total gastrectomy, a number of investigators[2, 7, 30, 50] showed that intestinal absorption of vitamin B_{12} is greatly increased by the simultaneous oral administration of intrinsic factor (in normal gastric juice or in desiccated hog stomach) with vitamin B_{12}.

SUMMARY

1. Among the causes of vitamin B_{12} deficiency in man is lack of intestinal absorption secondary to lack of the intrinsic factor necessary for the facilitation of this absorption. Intrinsic factor is secreted by gastric mucosa. Total gastrectomy removes the source of intrinsic factor.

2. The vitamin B_{12} deficiency state is manifested in many ways, but that most widely recognized is the clinical disorder better known as pernicious anemia.

3. The literature on the subject of total gastrectomy and pernicious anemia is reviewed.

4. The pathogenesis of this deficiency state is demonstrated in the reported clinical course of thirty patients subjected to total gastrectomy and followed for various periods of time from one to seventeen years after operation.

5. Among the earliest evidences of this deficiency state is macrocytosis of the erythrocytes. This appears from six months to two years after the operation. In the individual not given substitution therapy, other evidences of more profound deficiency appear in an orderly sequence, with anemia following macrocytosis, and megaloblasts developing in the bone marrow after the anemia

has appeared. Glossitis and other gastrointestinal signs appear when anemia occurs. Signs of central nervous system disease are observed only as a fairly late manifestation of the deficiency.

6. In light of the present knowledge of normal daily requirements of vitamin B_{12} and total body stores, the relative slowness of the deficiency state after gastrectomy is explained. Likewise, previously reported animal experimentation on total gastrectomy and hematopoiesis may be reinterpreted more meaningfully.

7. Substitution therapy can readily correct the deficiency state. Every patient subjected to total gastrectomy should receive vitamin B_{12} regularly after operation. At the present time to insure adequacy of therapy the parenteral route of administration is best; 45 mcg. of vitamin B_{12} intramuscularly every month is recommended for every patient who has had a total gastrectomy.

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Book Reviews

"Controlled Hypotension" in Anesthesia and Surgery. By David M. Little, Jr. Pp. 159. Springfield, Ill., 1956, Charles C Thomas. $4.50.

This book represents an abridged compendium of over 500 references on the subject of "controlled hypotension." The author discusses in detail the various techniques employed in the purposeful production of hypotension for the control of hemorrhage. The advantages and disadvantages of blood volume reduction, spinal and epidural blockade and ganglionic blockade are listed and compared. Both primary and secondary physiologic alterations are discussed in a systematic manner, giving the reader the necessary background material for a better understanding of the ensuing chapters.

The sections on complications, indications and contraindications are based on a review of 27,930 cases. The high mortality and morbidity incident to the hypotensive techniques dictated the meticulous manner in which these sections are set forth.

Finally, the tenets for the conduct of controlled hypotension are formulated—emphasis being placed on the lethal potential of this "physiologic trespass."

The contents of this book should be thoroughly digested by all those who contemplate subjecting patients to "controlled hypotension."

—F. H. Van Bergen

Urology. By B. G. Clarke and L. M. del Guerico. Pp. 235, with 162 illustrations. New York, 1956, Blakiston Division of McGraw-Hill Book Company. $6.50.

This is a small book intended primarily for medical students. The author of such a work is always confronted by many difficult decisions as to what to include and what to leave out, and there are likely to be some disagreements as to the decisions. According to the preface, this book "briefly presents the subject matter of Urology as an area in the study of general biology and medicine. . . ." The author enumerates five subsidiary purposes: (1) a short essential test, brief enough to be read during an undergraduate course in urology or used for reviews; (2) . . . reading made easy by using diagrams and pictures freely in place of textual material; (3) present a collection of x-rays and photomicrographs from cases of typical disorders; (4) present, in line drawings, some of the more important anatomic and surgical principles in urology; and (5) give a selected list of references to key books and articles on each disorder discussed in the text.

This little book is very well illustrated. The photomicrographs and most of the reproductions of x-rays are of high quality. It achieves the objectives set forth by the authors but is strictly for the harried medical student. It contains, by definition, too little detail for the resident or practitioner of urology. One cannot, for example, look up the details of surgical technique in it. It is recommended for its stated purposes.

—C. D. Creevy

The Cervical Syndrome. By Ruth Jackson, M.D. Pp. 130. Springfield, Ill., 1956, Charles C Thomas, Publisher.

This is a small monograph in which manifestations of some of the lesions involving the cervical roots are discussed. In the first part of the book a review of the anatomy and physiology of this region is given. Subsequent chapters discuss differential diagnosis and treatment. The emphasis is on the osseous and ligamentous structures and how they might compress the nerve roots. A mechanical basis for production of symptoms is the dominant theme. Case reports are used for illustration.

It seems to this reviewer that the monograph has value in that it discusses some data not readily found elsewhere. This is especially true of the section on anatomy, which is the principal chapter of the book. The chapters pertaining to clinical material seem incomplete.

It is felt the book's over-all usefulness would be greater had collaboration with a neurologist or neurological surgeon been obtained in its preparation. This would have permitted a wider perspective of the problem with less restricted concepts of diagnosis and treatment. Even so, the book is a worth-while contribution and is recommended for those physicians interested in this difficult clinical problem.

—Lyle A. French.

Complications of Regional Anesthesia. By Daniel C. Moore, M.D., Director, Department of Anesthesiology, Mason Clinic, Chief of Anesthesia, Virginia Mason Hospital, Seattle, Wash. Pp. 291. Springfield, Ill., 1955, Charles C Thomas. $10.50.

Again Dr. Moore has presented to the medical and dental professions an urgently sought, but heretofore, nonexistent text—*Complications of Regional Anesthesia.*

Surgical intervention in the aged, debilitated, and very "poor risk" patient has become commonplace. This fact alone has forced widespread adoption of the safest of all anesthetic techniques, conduction anesthesia. Consequently, an increased awareness of complications incident to regional anesthesia has become apparent.

Utilizing a style and layout similar to that employed in his book *Regional Block,* Dr. Moore has again effected a categorical and orderly management of the subject matter. This is particularly appreciated by readers since such a style lends itself well to rapid reading, easy comprehension, and quick reference.

Divided into three main sections, the book deals with complications of local infiltration, spinal and epidural block, and incidental techniques. Each complication is treated in its entirety; etiology, signs, symptoms, prophylaxis and treatment are discussed fully with appropriate editorial comment.

Considerable discussion is devoted to such manifestly important subjects as drug toxicity and potency, toxic reactions, accidental total spinal anesthesia, neurolytic agents, spinal headache, shock, and cardiac arrest.

This text is based on authentic data collected from the two largest regional anesthesia services in this country. No physician or dentist should attempt regional anesthesia without first having read *Complications of Regional Anesthesia.*

—F. H. Van Bergen.

Geriatric Anesthesia. By Paul H. Lorhan, M.D., Professor of Anesthesiology, Department of Anesthesiology, University of Kansas Medical Center, Kansas City, Kan. Edited by John Adriani, M.D., Director, Department of Anesthesia, Charity Hospital, New Orleans, La. Pp. 90. Springfield, Ill., 1955, Charles C Thomas. $3.25.

This monograph is of particular interest to the anesthesiologist and surgeon. As pointed out by the author, the average life expectancy of individuals is increasing. In addition, modern operative and anesthesia techniques offer such increased safety that surgical intervention in the aged and debilitated patient has become commonplace. It is most timely that such a treatise on geriatric anesthesia has become available.

Starting his monograph with a brief but pertinent section on the physiopathologic changes incident to old age, the author then proceeds to discuss in some detail the preoperative preparation of the geriatric patient. A brief chapter on operating room management follows, with emphasis on gentleness, proper positioning on the table, and protection of the skin overlying bony prominences. The following sections are devoted to a consideration of preanesthetic medication and anesthetic drugs, each of which are discussed from the standpoints of dosage, indications, and contraindications. Chapters then follow on the actual anesthetic management and care of the patient during the postoperative period.

Throughout this monograph, the ailments common to the aged are stressed. Specific methods for the preoperative preparation, anesthetic management, and postoperative care of patients with cardiovascular, pulmonary, hepatorenal, glandular, and central nervous system disorders are presented.

Easy to read, concise and factual, this book is a valuable addition to the American Lecture Series.

—F. H. Van Bergen.

Notice

Because of the large number of original communications awaiting publication in SURGERY, case reports are no longer being accepted.

—THE EDITORS.

Calendar of Surgical Meetings

1956

AMERICAN MEDICAL ASSOCIATION. *Clinical Session,* Nov. 27-30, 1956, Civic Auditorium, Seattle, Wash. Secretary, Council on Scientific Assembly, A. M. A., 535 N. Dearborn St., Chicago 10, Ill.

LATIN AMERICAN CHAPTER OF INTERNATIONAL SOCIETY OF ANGIOLOGY. *Third Meeting,* Nov. 8-11, 1956, Havana, Cuba. President, Armando Núñez Núñez, Calle 25 No. 510, Vedado, Havana, Cuba.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 4-6, 1956, the Boca Raton Club and Hotel, Boca Raton, Fla. Secretary, George G. Finney, M.D., 2947 St. Paul St., Baltimore, Md.

1957

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY. *Annual Meeting,* May 4, 6, and 7, 1957, The Palmer House, Chicago, Ill. Deadline for papers, Dec. 15, 1956. Secretary, H. T. Langston, M.D., 1919 West Taylor St., Chicago 12, Ill.

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS. *Annual Meeting,* May 1, 2, and 3, 1957, The Homestead, Hot Springs, Va. Secretary, John A. Taylor, M.D., 2 East 54th Street, New York 22, N. Y.

AMERICAN COLLEGE OF SURGEONS. Southern California Chapter. *Annual Meeting,* Jan. 18, 19, and 20, 1957, Biltmore Hotel, Santa Barbara, Calif. Secretary-Treasurer, Max R. Gaspar, M.D., 211 Cherry Avenue, Long Beach 2, Calif.

AMERICAN GYNECOLOGICAL SOCIETY. *Annual Meeting,* May 27, 28, and 29, 1957, The Homestead, Hot Springs, Va. Secretary, Andrew A. Marchetti, M.D., Georgetown University Hospital, Washington 7, D. C.

AMERICAN MEDICAL ASSOCIATION. *Annual Meeting,* June 3-7, 1957, Coliseum, New York, N. Y. Deadline for papers, Dec. 15, 1956. *Clinical Meeting,* Dec. 3-6, 1957, Auditorium, Philadelphia, Pa. Deadline for papers, July 15, 1957. Secretary, American Medical Association, George F. Lull, M.D.; Secretary, Council on Scientific Assembly, Thomas G. Hull, M.D.; address of both, 535 North Dearborn Street, Chicago 10, Ill.

AMERICAN SURGICAL ASSOCIATION. *Annual Meeting,* May 8, 9, and 10, 1957, The Palmer House, Chicago, Ill. Secretary, R. K. Gilchrist, M.D., 59 East Madison Street, Chicago 3, Ill.

AMERICAN UROLOGICAL ASSOCIATION. *Annual Meeting,* May 6-9, 1957, William Penn Hotel, Pittsburgh, Pa. Deadline for papers, Jan. 1, 1957. Secretary, Samuel L. Raines, M.D., 188 S. Bellevue Blvd., Memphis, Tenn.

THE CENTRAL SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 21-23, 1957, The Drake Hotel, Chicago, Ill. Deadline for papers, Oct. 15, 1956. Secretary, Charles D. Branch, M.D., 102 North St., Peoria, Ill.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 4 and 5, 1957, Mount Washington Hotel, Burton Woods, N. H. Deadline for papers, June 1, 1957. Secretary, Richard Warren, M.D., Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

THE PACIFIC COAST SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 4-6, 1957, El Mirador Hotel, Palm Springs, Calif. Secretary, Carleton Mathewson, Jr., M.D., Stanford University Hospital, San Francisco 15, Calif.

PAN-PACIFIC SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 14-22, 1957, Honolulu, Hawaii. Director General, F. J. Pinkerton, M.D., Room 230, Young Building, Honolulu, Hawaii.

THE SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 7-9, 1957, Columbus, Ohio. Secretary, James Hardy, M.D., Hospital of the University of Mississippi, Jackson, Miss.

THE SOCIETY FOR VASCULAR SURGERY. *Annual Meeting,* June 2, 1957, Hotel Biltmore, New York, N. Y. Secretary, Henry Swan, M.D., 4200 E. 9th Avenue, Denver, Colo.

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announcing

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